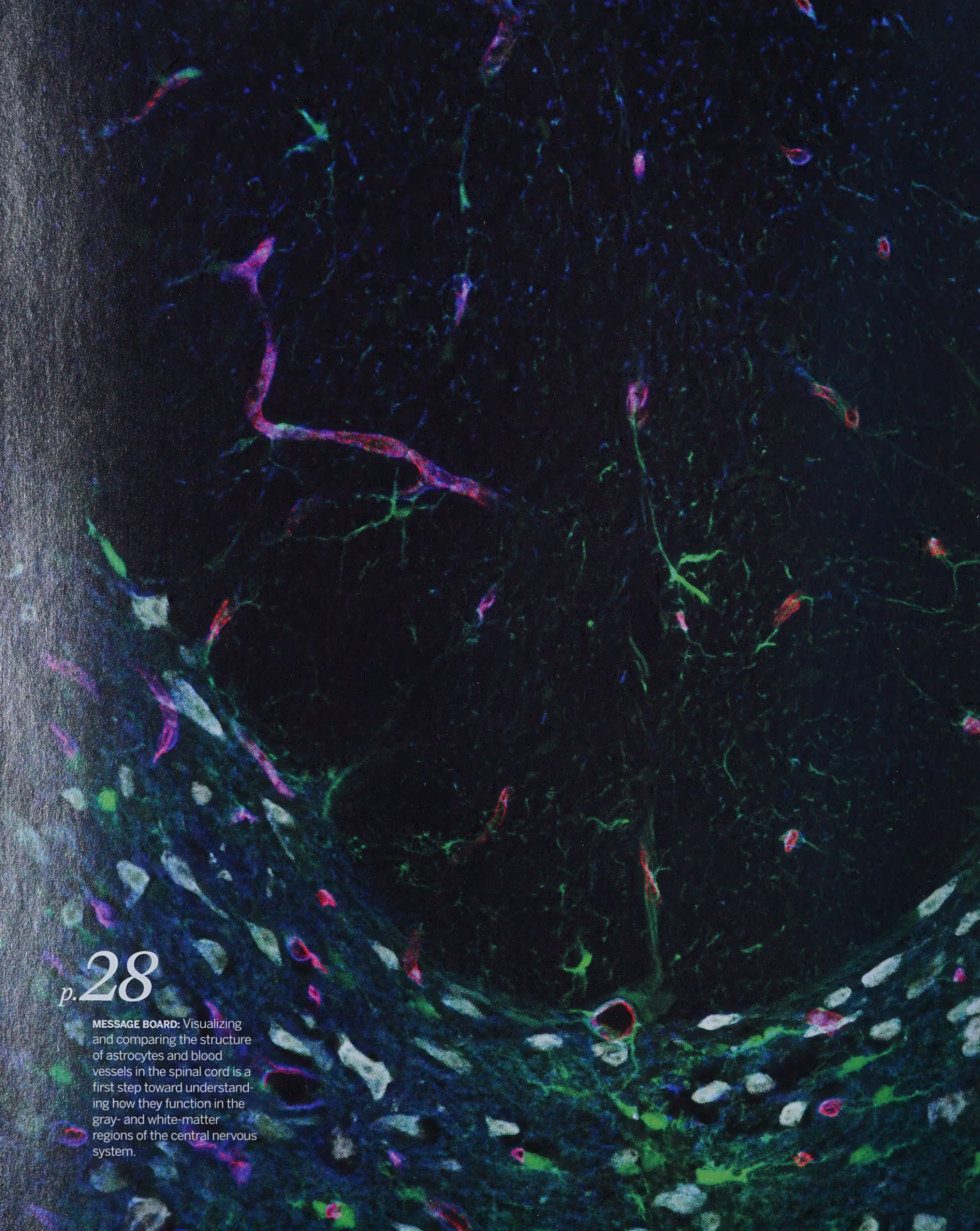
HARVARD medicine

AUTUMN 2018

Imaging: Science, Art, and Innovation



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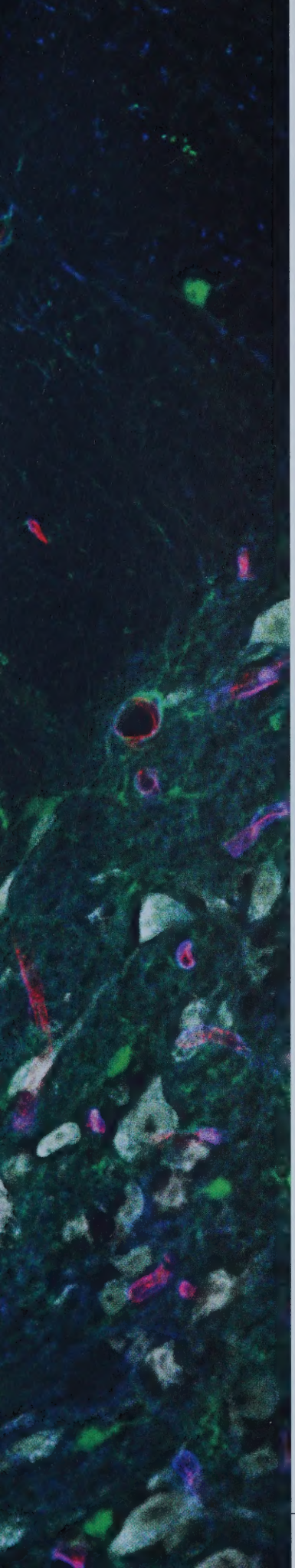
MESSAGE BOARD: Visualizing and comparing the structure of astrocytes and blood vessels in the spinal cord is a first step toward understanding how they function in the gray- and white-matter regions of the central nervous system.



ISLE BASTILLE

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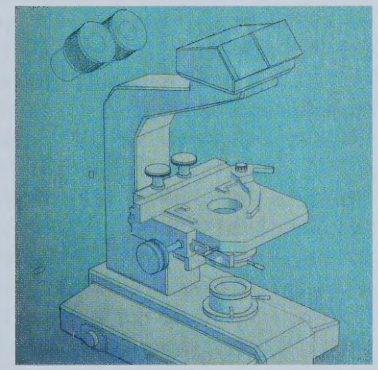

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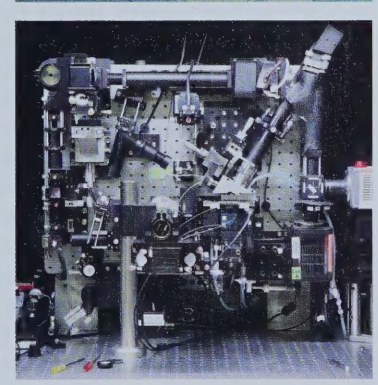

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Observing Is Learning

A GOOD PART OF OUR TRAINING as physicians and scientists is spent learning how to observe what is in front of us—and interpret it accurately.

Although the visual communication of science is not often discussed in scientific journals, its importance to the presentation of research findings was recently highlighted in a *Nature* blog. The contributor noted that images help present a "clearer scientific message," and "reduce uncertainty." Given that science crosses boundaries, experiences, and languages, a tool that reduces uncertainty is a currency of exceptional value.

Throughout HMS, there are hubs dedicated to creating, modifying, and maintaining a range of imaging tools, all in the service of visualizing science. One of these is our new cryo-EM facility, which allows investigators to elucidate molecular structures, a perspective necessary for achieving deep understanding of molecular mechanisms and designing novel therapeutics.

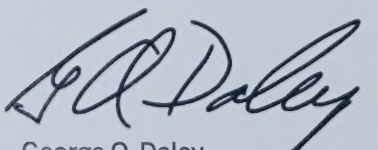
When existing tools aren't quite adequate for the task, scientists innovate. They tinker and they tweak. Sometimes, they simply build a tool from scratch. In fact, scientists are often as facile with circuit boards and hex wrenches as they are with experimental design and computational analysis.

When existing tools aren't quite adequate for the task, scientists innovate. They tinker and they tweak.

We recently invited our scientists to demonstrate how they use images to explain, illuminate, and celebrate their research. Faculty, trainees, and students shared images of the microscopic worlds they study and explained how their images articulate their research—and the beauty of life. Images came in from around the Quad—from cell biology, neurobiology, and microbiology, and from systems biology, genetics, and systems pharmacology.

Faculty who encouraged their students and trainees to participate in this exercise helped instill in our young researchers the value of communicating science and also underscored for them the importance of being scientifically "multilingual," of sharing their work to increase the appeal of science and access to scientific research.

It has always been necessary to communicate science visually—just recall the power of our first look at the helical structure of DNA. Presenting science clearly and dynamically is especially vital today as we work to further cultivate the public's engagement and understanding of the benefits of fundamental scientific inquiry.



George Q. Daley
Dean of Harvard Medical School

HARVARD medicine

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PHONE: 617-432-7878 | **FAX:** 617-432-0446
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RANDY GLASS

"The world needs a reminder of the existential threat nuclear weapons pose."

NEJM Reprise?

I READ THE SUPERB ARTICLE, "Chain Reactions" by Jake Miller, with great interest. I am delighted that *Harvard Medicine* chose to address this most important topic in its Winter-Spring 2018 issue.

HMS was indeed the center of the physicians' antinuclear movement, beginning in 1961 with the founding of Physicians for Social Responsibility (PSR) in Bernard Lowns' living room and, later, with the formation of the International Physicians for the Prevention of Nuclear War (IPPNW). These organizations have had a profound positive influence over the years, particularly during periods of heightened antagonism among the nuclear nations. And now, the world needs a reminder of the existential threat nuclear weapons pose, and more than ever, a sober assessment of this danger. It is the responsibility of physicians to play a major role by once again defining the health and environmental consequences of nuclear conflict.

The initial resistance of the medical profession to this effort was enormous. Organized medicine, and even some of my Harvard professors, confidently stated that "nuclear issues are the responsibility of the politicians, statesmen and generals, not doctors." It took a lot of convincing to change this attitude. The major architect of this change was Joseph Garland, MD 1919, then editor of the *New England Journal of Medicine*. Despite great resistance from his editorial board, in 1962 he published the series of articles titled "The Medical Consequences of Thermonuclear War," which is so well described in Miller's article. The response of the medical profession was astounding.

What can we physicians do now? Something that immediately comes to mind is to convince the editor of *NEJM* to republish the 1962 articles with added commentary by Ira Helfand, who is now a leader and a major voice of these organizations. I suspect this action might have a similar impact. Another is to convince medical schools to include nuclear issues and the medical consequences of a nuclear conflict in the regular curriculum. When I suggested this at our recent 60th reunion, it ignited great interest and enthusiasm. HMS should again be at the forefront of this issue.

Most important, perhaps, is the need to rekindle physician activism by joining and supporting PSR and IPPNW.

Finally, the world owes Helfand a great debt. He is tireless in his efforts and a most eloquent spokesman for this cause.

SIDNEY ALEXANDER, MD '57
FOUNDING MEMBER, PAST PRESIDENT OF PSR
CHESTNUT HILL, MASSACHUSETTS

Ed: Dr. Alexander asked to be placed in touch with Paula Michaels, a professor at Monash University in Australia quoted in Miller's article, in the hope that he might contribute to her research on the role of physicians in nuclear disarmament. We were able to fulfill his request.

A Place of Its Own

READING THE WONDERFUL ARTICLE on robotic limbs by Stephanie Dutchen in the Winter-Spring 2018 issue of *Harvard Medicine* prompted me to recall a reel-to-reel tape recording titled "The Boston Arm" that I have had for decades; it was lent to me when I was a resident at Beth Israel Hospital, now Beth Israel Deaconess Medical Center, in the 1960s.

I have been reluctant to discard the tape in case it contained useful archival information about this important contribution of Melvin Glimcher, MD '50. Yet, my attempts to locate a safe place for it have been unsuccessful.

Any help you might provide in salvaging the contents of this item would be appreciated.

DONALD LIPSITT
CAMBRIDGE, MASSACHUSETTS

Ed: We accepted Dr. Lipsitt's invitation—and are pleased we did. The tape captured a 1969 seminar, one in a series of seminars that year that explored advances in biology and engineering and their applications to medicine. The invited speakers were Melvin Glimcher; Robert Mann, an engineering professor at MIT; and Allen Cudworth, former director of research at Liberty Mutual Insurance. All had been involved in some aspect of the development of the Boston Arm. Dr. Lipsitt has generously agreed to donate the tape, its transcript, and an audio recording of its contents to the Melvin Glimcher collection at the Francis A. Countway Library of Medicine.

Strait Talk from Texas

I WANT TO THANK YOU for taking the time to locate a copy of the Autumn 2009 issue of the *Harvard Medical Alumni Bulletin*. I look forward to adding it to my collection of Houdini memorabilia.

I've collected material on Houdini for more than 40 years; my periodical collection alone contains more than 2,500 different items produced since 1898 in dozens of countries and languages. In addition to the periodicals, my collection includes posters, autographs, photos, handcuffs, and a straitjacket—more than 6,000 items in all, a number that never fails to surprise me.

The collection is my hobby and my passion. One aspect of my hobby that I truly enjoy is compiling a Houdini periodical bibliography that lists every printed magazine, journal, newsletter, and the like that contains a significant Houdini reference or article. It is the most in-depth resource for magic and Houdini aficionados that I know of. The next edition of this bibliography will include a citation listing for the article "The Illusionist," which appeared in the Autumn

2009 issue of your magazine and contains strong references to Houdini.

Thank you again for the copy of the *Harvard Medical Alumni Bulletin.*

ARTHUR MOSES
FORT WORTH, TEXAS

Ed: We were delighted to be able to contribute to Mr. Moses' collection and are especially pleased to know that stories from HMS reach far and wide over the years. Readers who are interested in learning more about Moses and Houdini can visit www.houdinispeaks.com.

A Goodbye to London

THE VALUE OF MENTORS and the role of great teachers at HMS came through clearly in the "Rounds" article in the Winter-Spring 2018 issue of *Harvard Medicine* magazine. I know how much I have valued the educational mentors I had throughout my academic career. One teacher in particular has been a source of friendship and wise counsel.

Earlier this year, I joined many others at a party marking the upcoming one-hundredth birthday of Irving London, MD '43, the founder and longtime director of the School's HST program and my mentor, teacher, and friend.

At the event, there were many brief speeches of appreciation, and Irv listened carefully to each. One of those was mine; it was the hardest speech of my life. How could I possibly thank him for everything in three minutes?

In his response, Irv said, "The talks that we have just been hearing are astonishing, and I've been listening with pleasure and wonderment and delight. Let me thank you all for being here. I feel certain that the future is bright and that HST will continue to flourish and be a source of great pride for all of us."

Later that evening, I drove with him to his home; he seemed so youthful in his hope for the future of medicine. I looked forward to seeing him again.

Now I, like so many, miss him terribly.

Irv represented everything that a teacher, a physician, and a friend embodies. He understood me as a student so many years ago, and after my student years, he was still there to give me strength and hope as only a mentor can. As I listened to others speak that evening, I realized Irv's interest and kindness came to each of us in many different ways and at different phases of our education. He had a gift for understanding the human condition and the ability to give more, more, more. Those of us fortunate enough to have been chosen for his program know fully how enormous a difference his life made in ours.

Now the challenge for those of us who remain will be to help HST continue to uphold his legacy.

SHARON ANN CLARK, MD '80
SAN MATEO, CALIFORNIA

Ed: In the Spring 2016 issue of Harvard Medicine, *Dr. Clark wrote about the HST program, its importance in her life and career, and her bond with Dr. London. We invite readers to revisit her article at magazine.hms.harvard.edu/surgery/view-london.*

Cut Diamonds

THE "REFLECTIONS" ARTICLE in the Winter-Spring 2018 issue of *Harvard Medicine* magazine came to my attention just as I was preparing to gather with classmates for our 60th reunion. Seeing the names and faces of faculty who have shaped the School provided a good segue to my get-together with classmates who shaped my years at HMS, whose collegiality has shaped my life, and whose work has helped shape medicine.

For each of our reunions, the HMS Class of 1958 gathers away from the Longwood campus. This year, our class congregated for four days (May 20-24) in nearby Salem at the historic Hawthorne Hotel. By all accounts, it was a jolly occasion.

Classmate **George Jacoby** arranged a series of events that included a presentation of the exciting new changes at the Peabody Essex Museum and a tour of the House of the Seven Gables, its gardens, and the surrounding historic buildings celebrating Nathaniel Hawthorne. We also enjoyed a schooner voyage around Salem and Marblehead.

It seems that time has made speechmakers of us all, each hoping someone is listening, possibly even comprehending, our orations. There were, fortunately, formal presentations for us to enjoy, too. David Torchiana, MD '81, a world-renowned cardiac surgeon who is now the head of Partners HealthCare, described some of the issues facing medicine today. He was insightful and informative. Classmate **Richard Rieselbach** discussed his program to bring academic care and education to a geriatric community. A presentation by invited speaker Jules Dienstag, the former HMS dean for education, took us through the thinking behind the recent changes to the HMS curriculum. This presentation generated a spirited discussion.

To bring a touch of local history to our gathering, I presented some new views on the witchcraft tragedy that occurred in Salem in 1692 and talked about research showing the role of hysteria as well as revelations about the nefarious participation of a local minister.

As for each of our reunions, the high point is the inspirational lecture to the graduating class, a lecture endowed by our class several years ago. This year's lecture, titled "The Noble Calling," was delivered by our classmate **Elliott Miller**. In it, he emphasized the great opportunity that physicians have to give of their time and talent to society and illustrated some of those opportunities with examples from his life.

Planning these gatherings always require a good deal of heavy lifting. This year's reunion committee relied on the already-mentioned talents of George Jacoby as well as those of **Thorne Winter III**, **Cecil Coggins**, and our class treasurer, **Peter Schur**. Our committee chair and class agent, who deserves maximum kudos, is **Howard Corwin**. A special thanks to our famed class president, **Joseph Burnett**.

ANTHONY PATTON, MD '58
TOPSHAM, MAINE

Ed: We're grateful to Dr. Patton for sharing news of his reunion with us. His letter continues our tradition of telling the stories of HMS doctors.

Alarm Bell

CANCER CELLS express unusually high levels of TRPA1, a calcium channel protein. Research by cell biologists at HMS recently showed why: Tumor cells use TRPA1 to defend against toxic cellular byproducts known as reactive oxygen species.

Normally, TRPA1 acts to alert the body to environmental irritants that could be harmful. Eat something exceptionally spicy, for example, and tears may follow in reaction to TRPA1's alarm. This response has earned TRPA1 the nickname "the wasabi receptor."

Not only do the findings show how critical a defense against oxidative stress is to cancer's progression, they also offer insight into the protein's role in the disease and, possibly, in new treatments.

Brugge JS, et al., *Cancer Cell*, June 2018

Wasabia japonica is a member of the Brassicaceae family. Here, fresh stems of the plant have been trimmed and prepared for sale.

Colorized scanning electron micrograph of *Escherichia coli*, a bacterium commonly found in the lower intestines of humans and other animals.

The Power of One

RESEARCHERS studying the human microbiome face a chicken-and-egg problem when comparing the bacterial mix from a healthy gut with that from a diseased gut: Do they attribute any differences to the disease changing the microbiome or the microbiome changing and altering the host health or disease state? HMS scientists, probing how molecules produced by gut bacteria influence mouse metabolism, found that the deletion of a single gene in a strain of the *Bacteroides* bacterium caused significant metabolic changes and lowered weight gain in the animals. The finding is an early step in work toward developing treatments for metabolic diseases that target the microbiome.

Devlin AS, et al., *eLife*, July 2018

NIAID/NIH

IMMUNOLOGY

TB vaccine lowers blood sugar in type 1 diabetes

HMS SCIENTISTS at Massachusetts General Hospital have shown that the BCG vaccine, used for more than a century to prevent tuberculosis, appears to control blood-sugar levels through a metabolic mechanism that increases cellular consumption of glucose. This mechanism shifts glucose metabolism from oxidative phosphorylation, the most common pathway by which cells convert glucose into energy, to aerobic glycolysis, a process that involves significantly greater glucose consumption by cells.

In addition to pointing to a possible way to safely stabilize blood sugar at near-normal levels, the findings show how a limited dosing protocol could make permanent, beneficial changes to the immune system while lowering blood-sugar levels.

For the study, a group of adults with long-standing diabetes received two courses of the vaccine. Three years after the administrations, the blood-sugar levels of the participants returned to near-normal and remained normal for five years.

Regular monitoring of vaccine recipients revealed another benefit: their HbA1c levels dropped by more than 10 percent three years after treatment and by more than 18 percent four years after treatment. This reduction held for another four years.

It has been known for more than 30 years that BCG boosts the production of tumor necrosis factor. This factor may be beneficial in autoimmune diseases both because it eliminates the autoreactive T cells that attack an individual's tissues—in the case of type 1 diabetes, pancreatic islets—and because it induces the production of regulatory T cells that could prevent an autoimmune reaction.

A separate mouse study showed that BCG reduced blood-sugar elevations caused by means other than autoimmune attack, raising the possibility that BCG vaccines could also be beneficial against type 2 diabetes.

Kühtreiber WM, et al., *npj Vaccines*, June 2018

Neurobiology

Interplay of two types of neurons found to be key to coordinated movement

Mouse studies show that the brain's coordination of discrete movements into a continuous sequence, such as for dance, results from the balanced action of two types of neurons in the striatum. The results could inform our understanding of Parkinson's disease and other neurodegenerative conditions that affect movement.

Datta SR, et al., *Cell*, June 2018

SYSTEMS REGULATION

Inner-ear pressure maintained by tiny pulsations

USING TIME-LAPSE MICROSCOPY to study the inner ear of zebrafish, HMS scientists in the Department of Systems Biology found that a tiny inner-ear structure pulsated, inflating and deflating with a remarkable regularity. The pulsating structure, they discovered, was the endolymphatic sac, a fluid-filled pocket that connects to the rest of the inner ear by a long, thin duct.

The inner ear, responsible for hearing and balance, is composed of several complex interconnected structures filled with a fluid that moves in response to sound waves or head movement. The fluid's subtle movements are detected by sensory cells and converted into neural signals for the brain to process.

Both the pressure and chemical composition of inner-ear fluid must be carefully maintained. In fact, certain disorders, such as the vertigo-inducing Ménière's disease, are thought to stem from abnormal pressure fluctuations.

Although long thought to be involved in regulating this fluid, the endolymphatic sac in humans has been hard to study: The inner-ear structures in mammals are small and encased in dense bone. The inner-ear structures of zebrafish, however, are easily visible.

The team's analysis revealed flap-like membrane projections extending from the cells that make up the endolymphatic sac. These flaps overlap each other, forming what are called lamellar barriers.

By using technology that captures 3D images and movements of cells in living organisms, the scientists saw the lamellar barriers dynamically moving. As fluid pressure builds, the sac inflates, and the barriers begin to separate. Once a certain point is reached, the barriers open, allowing fluid to flow out of the sac to lessen the pressure.

The team thinks such a mechanism may be present in other structures that also contain pressurized fluid-filled cavities, such as the eye, brain, and kidneys. Knowing the actions of these cavities, and perhaps how to control them, could inform new treatments for conditions such as glaucoma.

Swinburne IA, et al., *eLife*, June 2018

HEALTH POLICY

Doctors' end-of-life care for cancer patients varies

THE TYPE AND DURATION of end-of-life care for patients with terminal cancer differs strikingly across the United States, according to work by HMS researchers in the Department of Health Care Policy. The study, which looked at people with end-stage lung and colorectal cancers, showed that in some regions, care for patients in the last month of life increased in intensity. In some areas, this level of intense care resulted in spending twice that for similar patients elsewhere. »

» The variations, the researchers say, did not stem from patients' beliefs and preferences. Instead, they were attributed to differences in physicians' beliefs about end-of-life care, their style of practice, and the availability of regional health care services.

Physicians in areas with higher spending reported feeling less prepared for and less knowledgeable about the care of patients with terminal cancer. Doctors in these areas were more likely to suggest chemotherapy for patients unlikely to benefit from the treatment because of poor health status, and these physicians were less likely to discuss do-not-resuscitate or hospice options with patients. The doctors also reported being less likely to seek hospice care for themselves if they were to become terminally ill with cancer.

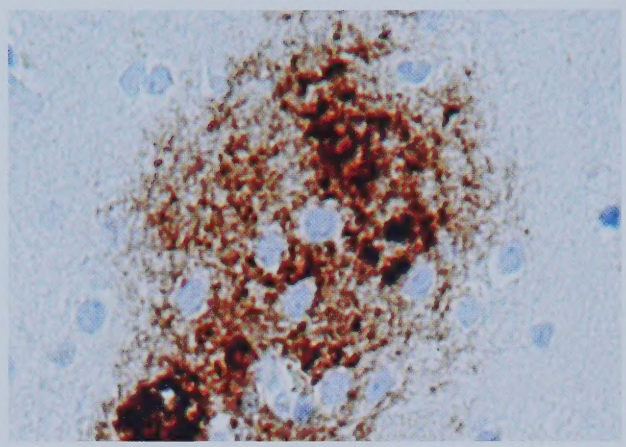
A growing body of evidence shows that, for cancer patients, additional end-of-life care does not contribute to better outcomes. The findings, the researchers say, underscore the need for better physician education and training aimed at increasing doctors' comfort with both addressing end-of-life issues and delivering appropriate levels of care.

Keating NL, et al., *Health Affairs*, July 2018

AGING

Mutations raise risk for white blood cell disorder

SOME OF THE FIRST known inherited genetic variants that significantly raise a person's likelihood of developing clonal hematopoiesis have been identified by researchers at HMS and the Harvard T.H. Chan School of Public Health. This age-related condition is marked by the accumulation of genetically abnormal white blood cells. Such cells may become cancerous or contribute to inflammation in atherosclerotic plaques, a potent risk factor for heart attacks and strokes.



Amyloid beta plaques (brown) in the cerebral cortex are a hallmark of Alzheimer's disease.

The researchers note that although clonal hematopoiesis is increasingly seen as an important biomarker of risk for future illness, little has been known about what causes the condition. The study brings new clarity by showing the specific sequence of genetic events that give rise to the abnormal blood cells. It also shows that inherited and acquired mutations are more connected than previously thought.

Acquired mutations are thought to occur randomly over time by either appearing spontaneously or after exposure to damaging agents such as ultraviolet light. Yet the team found examples where inherited variants led to the appearance of specific acquired mutations later in life or gave white blood cells with such mutations a growth advantage over other cells.

Clonal hematopoiesis occurs when a single blood stem cell acquires mutations that cause it to produce more than its share of new cells, including white blood cells. Over time, the mutants outcompete normal blood cells, either by proliferating more rapidly or surviving longer. These genetically dominant blood cells are called clones.

With more research, scientists will be able to better assess the risks each clone confers and use that knowledge to develop environmental or medical interventions that might slow the growth of clones and avert disease.

McCarroll SA, Price AL, et al., *Nature*, July 2018

NEUROLOGY

Herpes protection triggers Alzheimer's in mice

AMYLOID BETA, the protein deposited as plaques in the brains of patients with Alzheimer's disease, has been shown to protect the mouse brain from the effects of herpesviruses.

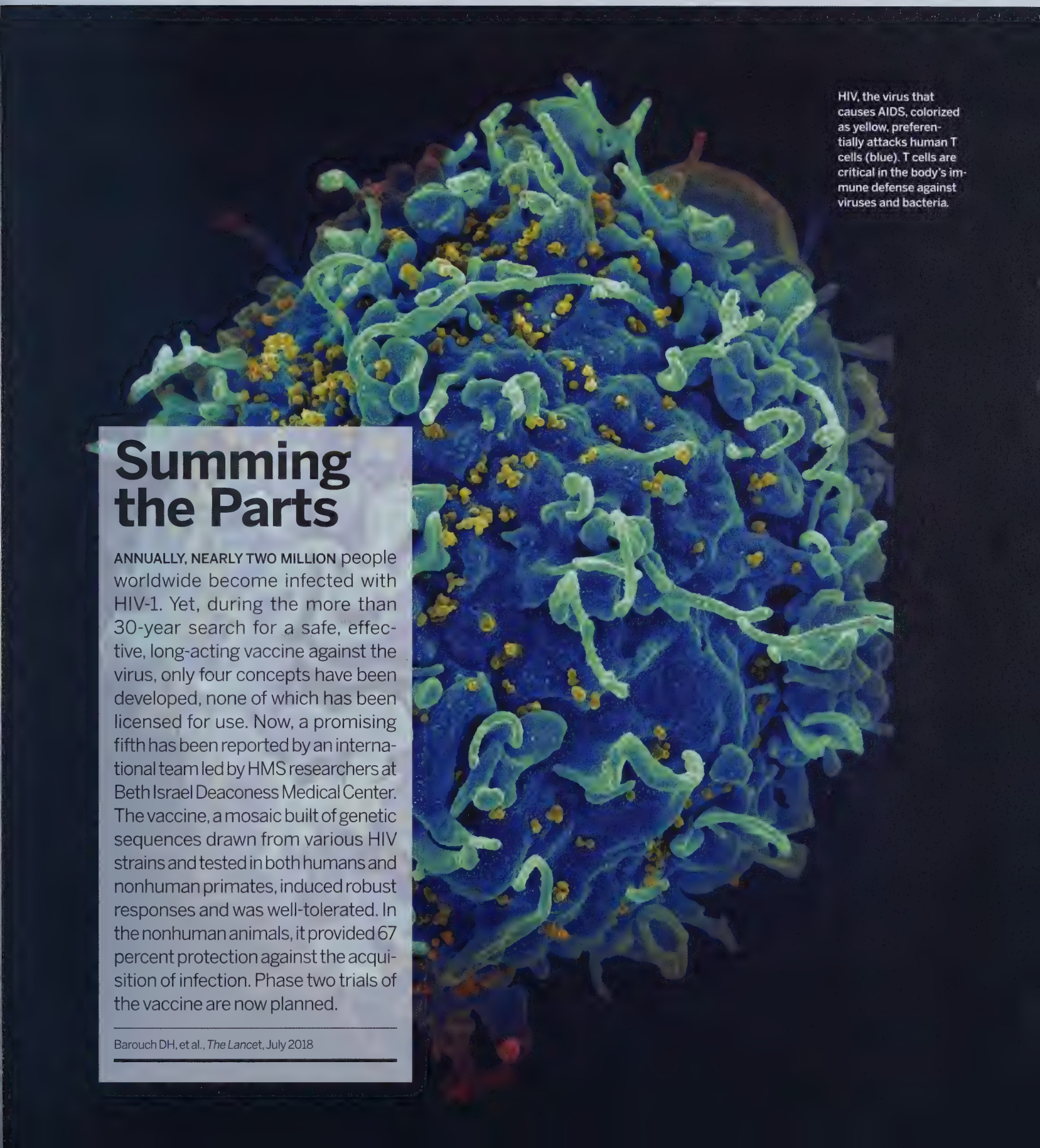
Research by HMS scientists at Massachusetts General Hospital has revealed a simple and direct mechanism by which herpes infections accelerate the deposition of amyloid beta proteins in the brain and, in turn, accelerate the progression of Alzheimer's disease.

Brain infection with herpes simplex, the virus that causes cold sores, is known to increase with aging, leading to an almost universal presence of that and other herpes strains in the brain by adulthood.

Over the years, multiple epidemiological studies have suggested that people with herpes infections are at higher risk for Alzheimer's disease. The recent study, say the researchers, merges the infection hypothesis with the amyloid hypothesis, forming what they refer to as the antimicrobial protection hypothesis of Alzheimer's.

Taken together with results from a recent study out of the Icahn School of Medicine at Mount Sinai, the HMS findings suggest that a treatment model that would use both antiherpes and antiamyloid drugs could be effective against early Alzheimer's disease. Furthermore, the scientists say, as neuroinflammation gets underway, there may be a greater benefit in targeting inflammatory molecules. More research will be needed before any such treatment approaches could be considered. Although the findings are intriguing, it remains unclear whether infection is the root cause of Alzheimer's.

Eimer WA, et al., *Neuron*, July 2018



HIV, the virus that causes AIDS, colorized as yellow, preferentially attacks human T cells (blue). T cells are critical in the body's immune defense against viruses and bacteria.

Summing the Parts

ANNUALLY, NEARLY TWO MILLION people worldwide become infected with HIV-1. Yet, during the more than 30-year search for a safe, effective, long-acting vaccine against the virus, only four concepts have been developed, none of which has been licensed for use. Now, a promising fifth has been reported by an international team led by HMS researchers at Beth Israel Deaconess Medical Center. The vaccine, a mosaic built of genetic sequences drawn from various HIV strains and tested in both humans and nonhuman primates, induced robust responses and was well-tolerated. In the nonhuman animals, it provided 67 percent protection against the acquisition of infection. Phase two trials of the vaccine are now planned.

Barouch DH, et al., *The Lancet*, July 2018

noteworthy

HMX to collaborate with Meharry on medical education offering

An online education tool developed at HMS is now being offered to first-year students at Meharry Medical College, one of the nation's oldest and largest historically Black academic health science centers.

The coursework, part of the HMS online learning program, HMX Fundamentals, focuses on subjects deemed fundamental for all frontline clinicians, not just specialists.

This collaboration will allow incoming medical students at Meharry to take online courses in genetics and physiology the summer before they arrive on campus.

"We want to use this unique educational material to inspire budding physicians and build on their passion for biomedical science," says David Roberts, MD '95, HMS dean for external education (*fig. 1*). "Incoming HMS students have already used the courses to prepare for the demanding curriculum ahead of them, and the results and feedback show that this prep makes a difference."

HMX courses are currently offered to students at HMS and the Harvard School of Dental Medicine, as well as through institutional partnerships around the globe in which students use the material to prepare for medical-training programs.

The program features real-life case studies and offers an immersive experience, veering away from traditional passive learning and slideshow presentations. Students are exposed to actual medical scenarios filmed in clinical settings, such as intensive care units and cardiac catheterization labs at Harvard-affiliated hospitals, allowing them to work through real-life applications of concepts.

Each course features an interactive forum where students can ask questions about the content and receive expert feedback.

In a marked departure from traditional lecture-based learning, the program's courses include scenarios that present complex topics in relevant clinical contexts.

"We're building a learning experience around topics that are pivotal for the future of medicine and patient care," says Michael Parker, associate dean for online learning and faculty director of HMX. "Reaching learners as they prepare for the demands of a challenging curriculum will be crucial to their success."

New approach to regulatory science, cancer therapeutics

The systems used to develop new drugs and evaluate their efficacy are ripe for reinvention, and two new centers within the Harvard Program in Therapeutic Science are up to the task.

The Harvard-MIT Center for Regulatory Science aims to transform the science of therapeutic development and streamline the process of evaluation, approval, and regulation to help nurture (*fig. 2*) and advance efforts to bring forward new medicines while trimming costs.

The National Cancer Institute Center for Cancer Systems Pharmacology will employ a multidisciplinary systems approach to the study of cancer therapies. It will pool the collective talents of basic scientists, translational researchers, clinical oncologists, pathologists, and computational scientists from five institutions to help refine our understanding of the interaction between the immune system and cancer, boost the efficacy of current cancer immunotherapies, and spark the development of new treatments.

The centers are located in the Laboratory for Precision Medicine and Regulatory Science, a multi-institutional space designed to bring together scientists from a range of disciplines in academia, industry, and government.

"These two new centers are a continuation and an extension of Harvard Medical School's überstrategy to better integrate the translation of the wonderful science that happens at HMS and across Harvard and bring it to patients," said Joshua Boger, a member of the School's Board of Fellows and the founder of Vertex Pharmaceuticals, at the opening ceremony for the centers. "This is not merely a new lab—it is a new model of collaboration."

fig. 1

fig. 2

fig. 3

Dialogues provide safe spaces to discuss diversity issues

As part of the overall effort to foster diversity and increase conversation on diversity and inclusion issues on campus, the School has been sponsoring a series of events meant to encourage a productive exchange of ideas about diversity in the community. These events are part of the School's ongoing commitment to assess and support diversity and inclusion at HMS.

The HMS Diversity Task Force, established by George Q. Daley, MD '91, and made up of faculty, students, staff, and administrators from across campus, is being led by Joan Reede, HMS dean for diversity and community partnership and professor of medicine (*fig. 3*). Among the programs the group has initiated is a series of dialogues. A recent occasion, "Being Other," brought together members of the HMS community to discuss what it has meant to be in a minority at the School.

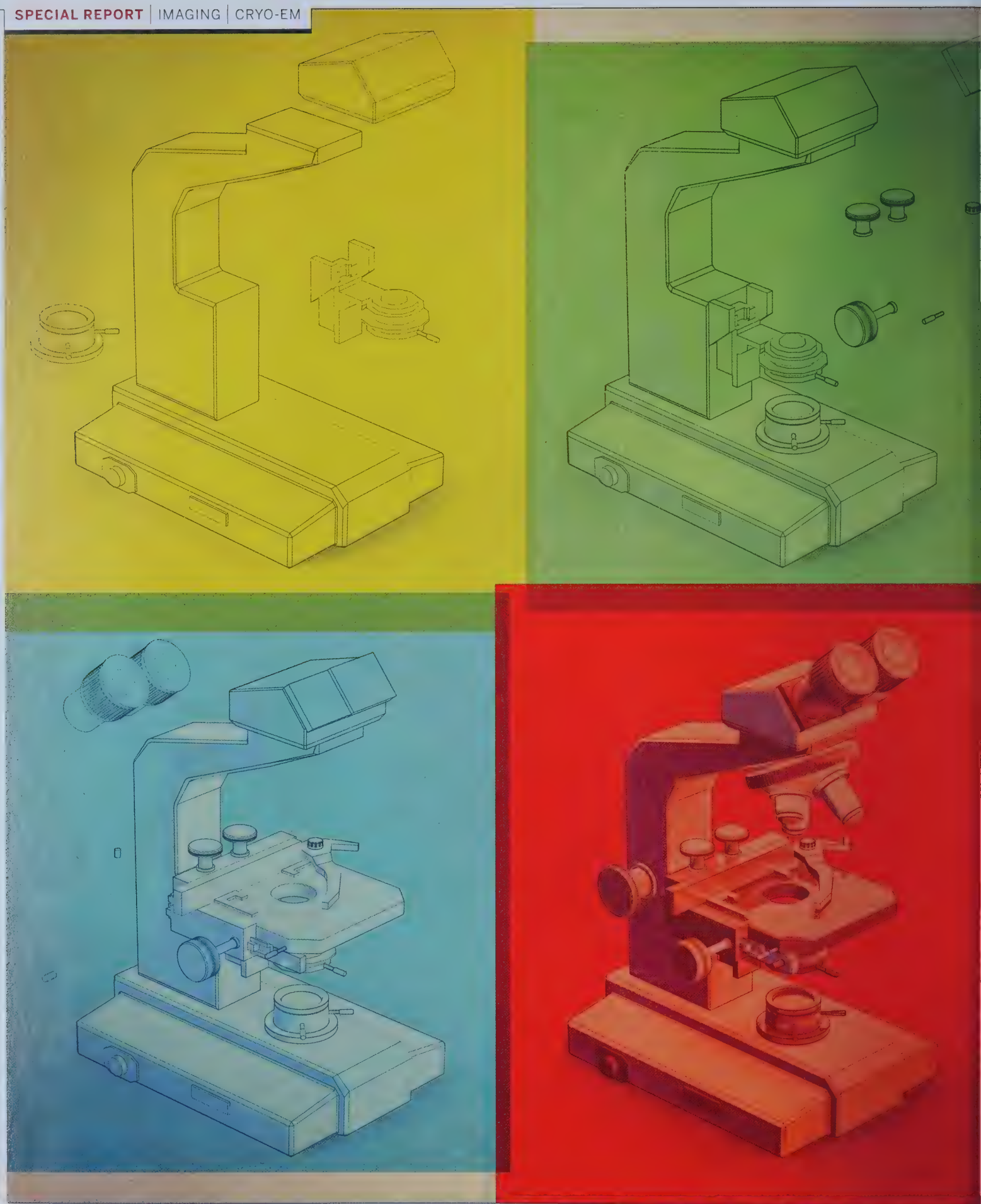
Reede began the conversation by sharing her experience of being a Black woman in a predominantly white medical school. She encouraged the group to think about the questions that come with this complicated topic, such as what it means to feel out of place.

"It was wonderful to have individuals from around the HMS community come together to share their own stories of being other," Reede said after the event. "This event allowed new perspectives to be heard and meaningful dialogue to take place."

According to Sergio Núñez-Báez, MMS 2019, a graduate student in immunology, the Dialogues series represents a new kind of safe space at the School. "You cannot solve things until you put them out there," he said.

The Worlds Within

Nearly four hundred years ago, Italian scientists Federico Cesi and Francesco Stelluti peered through the eyepiece of an instrument designed by Galileo and saw, in startling detail, the anatomical structures of a bee. A few years later, Stelluti published drawings made from their observations. That book, *Persio*, was the first to feature images of objects seen through a microscope. In the pages that follow, we continue that tradition by showing the worlds our scientists discover when they use technology to see the unseen.



A Better Look

BY KEVIN JIANG

The development of cryo-EM has revolutionized structural biology by offering a deeper view of structure and function

Eric Fischer hadn't intended to help figure out the biological mechanism of one of the more infamous drugs in history. Nor had he envisioned playing a role in sparking a new field of drug development. He had just wanted to see what thalidomide looked like in action at the atomic level. He was, after all, training to become a structural biologist.

"We looked at it out of pure curiosity," recalls Fischer, now an HMS assistant professor of biological chemistry and molecular pharmacology at Dana-Farber Cancer Institute. "It was fascinating that there was so little known about its mechanism of action."

When thalidomide hit German pharmacies in 1957, the over-the-counter sedative became an instant blockbuster. Marketed as a wonder cure for insomnia and morning sickness, it was said to be so safe that scientists "could not find a dose high enough to kill a rat." Soon, it was being distributed in forty-six countries, often to pregnant women.

Then,

wonder turned to horror: As a result of in utero exposure to the drug, more than 10,000 children in Germany alone were born with devastating birth defects. By the early 1960s, thalidomide was being frantically pulled off the world market.

This tragedy raised many scientific questions. How did thalidomide cause the malformation of arms, legs, and organs during fetal development? How did the drug, as clinical trials later revealed, slow the growth of cancers such as multiple myeloma, for which the drug is now a frontline treatment? The answers eluded scientists for decades.

An important clue came in 2010 when researchers discovered that thalidomide binds to a component of a certain form of ubiquitin ligase that cells use to tag proteins for destruction. For Fischer, this discovery proved timely. He happened to be studying the molecular structure of ubiquitin ligase using the workhorse of structural biology, x-ray crystallography.

Fischer and his colleagues painstakingly purified and crystallized the specific ubiquitin ligase bound with thalidomide, and then blasted it with x-rays. They used the pattern that formed as the x-rays passed through the crystal to deduce the arrangement of its atoms—the same technique Rosalind Franklin employed in the 1950s to generate the data used to solve the structure of DNA.

Every day, researchers reveal more of the molecular processes that underpin life.

After some data crunching, the researchers saw something interesting: a nearly imperceptible handful of atoms nestled in a tiny pocket on an enormous protein complex.

They had located the thalidomide.

Like a speck of dust in the delicate gears of a watch, thalidomide's presence was enough to perturb the function of the ubiquitin ligase. One of the complex's normal targets could no longer bind in that pocket. Instead, thalidomide caused the ubiquitin ligase to selectively bind, and mark for destruction, other proteins, specifically a set of transcription factors known to play a role in multiple myeloma.

As the master regulators of a cell's biology, transcription factors play central roles in almost every disease imaginable, from cancer to cardiovascular disease to Alzheimer's. But, says Fischer, they were considered undruggable.

"The idea of selectively degrading transcription factors has been around for a long time, but no one could ever get it to work," Fischer says. "An understanding of thalidomide's mechanism has shown that this is in fact very much possible, and by manipulating this mechanism, we could potentially develop new drug candidates.

"I don't think there's a big pharmaceutical company out there that's not exploring this opportunity."

Throughout history, observations of structure, from Hooke's cells to the beaks of Darwin's finches, have provided insights necessary to understand how life works. This is particularly true in structural biology, a discipline focused on visualizing life at its most fundamental. Discoveries of the atomic structures of important proteins and biological molecules have been among the most celebrated in science and have generated more than a dozen Nobel Prizes, new fields of research, and multibillion-dollar companies.

Despite their successes, structural biologists have struggled to keep pace as technology transforms the study of biology. Every day, researchers reveal more of the molecular processes that underpin life, and biopharma companies, racing to manipulate newly discovered biological targets, pop up like mushrooms. The tools that structural biologists have relied upon were developed decades ago, so the functional mechanisms of these myriad new molecules often remained invisible.

How many other thalidomides wait to be seen?

So, when researchers began publishing near-atomic resolution structures of complex proteins using a technique known as cryo-electron microscopy (cryo-EM) in the early 2010s, structural biologists around the world declared, without hyperbole, that a revolution had begun.

Ahead of its time

In 2015, the journal *Nature Methods* named cryo-EM, which involves flash freezing molecules and imaging them with an electron microscope to deduce their structure, the Method of the Year. In 2017, cryo-EM pioneers received the Nobel Prize in Chemistry. National Institutes of Health director Francis Collins has blogged about its implications for drug discovery. To many, scientists and nonscientists alike, the technology seemed to emerge from nowhere. Yet structural biologists knew it had been decades in the making.

"The triumph of twentieth-century biology was discovering that cells speak the

The number of biological structures mapped using electron microscopy techniques is growing. According to the Electron Microscopy Data Bank, in 2015,

114

of all structures submitted to this public database mapped to resolution levels better than 4 Angstroms—the resolution levels achievable with cryo-EM. As of early August 2018, the Data Bank had received

322

maps that achieved such resolution.

Hao Wu

language of chemistry and that the structure and interaction of molecules determine the phenomena that we call biology," says structural biologist Stephen Harrison, PhD '68, the HMS Giovanni Armenise-Harvard Professor of Basic Biomedical Science.

"Cryo-EM is critical to how we will translate those lessons into knowledge that broadens our understanding of biological processes and helps us solve important problems in medicine in the decades to come," adds Harrison, who is the director of the Harvard Cryo-EM Center for Structural Biology, a new facility jointly established by HMS, Harvard's Office of the Provost, Boston Children's Hospital, Dana-Farber Cancer Institute, and Massachusetts General Hospital.

Theory and practice

Despite being one of the most productive scientific tools in history, x-ray crystallography has limitations. Coaxing a protein to form a large, perfectly aligned crystal—like a brick made up of the same repeating component part—is unpredictable and can take years of empirical testing to achieve.

Many proteins, either because of their complexity or composition, simply cannot be crystallized. Even when the process is successful, crystal structures fix a protein in an unnatural state and offer little insight into the protein's different conformations and interactions.

It was his frustration with x-ray crystallography that drove structural biologist Richard Henderson, who shared the 2017 Nobel Prize in Chemistry for his contributions to cryo-EM, to seek alternatives in the 1970s.

"The specimen we had wasn't working with x-rays, so we thought we'd try something else," says Henderson, who is based at the MRC Laboratory of Molecular Biology in Cambridge, England.


Maofu Liao

Henderson turned to electron microscopes, which fire a beam of electrons that interact with the atoms of the sample they pass through. These interactions are picked up by an electron detector and used to create a highly magnified image of the sample.

In 1975, Henderson and his colleague, Nigel Unwin, became the first to use an electron microscope to derive the 3D structure of a protein crystal. Although the work established proof of principle, the resolution remained far from that achieved through x-ray crystallography. Still, Henderson and others pushed forward.

In the early 1980s, Henderson's fellow 2017 Nobel laureate, Jacques Dubochet, now at the University of Lausanne in Switzerland, put the "cryo" in cryo-EM when he developed a way to flash freeze a sample of a purified protein in solution. This process preserved the natural atomic state of the protein and held the molecules nearly motionless so they could be imaged. Scientists suddenly did not need to crystallize samples to see individual isolated proteins.

Yet, without crystallization, a protein of interest orients randomly throughout a solution, producing a confusing mess that is difficult to analyze.

Fortunately, the third of the 2017 Nobel laureates, Joachim Frank, currently at Columbia University in New York, was already working on a solution. He was developing sorting algorithms that could process images of thousands of individual, randomly oriented molecules and group them by shape. By averaging similarly shaped groups together, Frank could reconstruct 2D images of a protein from essentially every point of view. These 2D images could then be composited into a 3D model of the protein being studied.

By the 1980s these innovative approaches had effectively created cryo-EM as it exists today. It took decades, however, before it became clear whether cryo-EM would ever be a broadly useful technology. A key moment came in 1995, when Henderson calculated and published a seminal review outlining what was needed to achieve atomic resolution with cryo-EM.

"From then on our goal was to realize what the theory suggested we should have," says Henderson.

"So, for 20 years, we've known that cryo-EM was going to work," he adds. "It just needed technical problems to be solved."

They also had to wait for the smartphone to be invented.

Camera work

Like many researchers, Hao Wu, the HMS Asa and Patricia Springer Professor of Structural Biology at Boston Children's Hospital, turned to cryo-EM out of necessity. Her lab studies signaling proteins, particularly ones that cells use to coordinate the body's innate immune response. These proteins are essentially alarm bells, recruiting immune cells and promoting inflammation when a foreign invader is detected. Understanding their structure and functional mechanisms is critical, Wu says, since inflammation not only can be damaging but is also increasingly being linked to diseases from cancer to neurodegeneration.

A few years ago, when cryo-EM was still being derided as "blobology" because of the low-resolution, blob-like structures it produced, Wu discovered that the signaling proteins she was studying formed complexes that could not be crystallized. The complexes were also too large to be analyzed using the other primary structural biology tool, nuclear magnetic reso-

"I'm very optimistic about the future of cryo-EM, not because it will help us discover more new structures, but because it will allow us to directly visualize function."

nance spectroscopy. To gain the structural insights needed to develop new therapeutic strategies against the diseases in which these proteins may be involved, Wu needed an alternative.

"Our move to cryo-EM was driven by biology, not technology," Wu says. "I think we were in the right place at the right time—suddenly cryo-EM became so much better."

That improvement spun from a new generation of image sensors developed in response to consumer demand for better cell phone cameras. A number of key players, including Henderson, worked with manufacturers to leverage new sensor technology into greatly improved direct electron detectors for cryo-EM. These new detectors could even take movies. Movies allowed for the computational rectification of movement, induced by the energy of the electron beam, that occurred in a sample. The result: blur-corrected images.

Much better

Combined with dramatic increases in computational power and improved algorithms, cryo-EM specialists could now generate hundreds of thousands, even millions, of blur-corrected images of a protein and use them to calculate 3D atomic models relatively quickly. Formerly blurry models soon revealed functionally important side chains. The resolution revolution had begun.

"When you know which atom is next to which atom, it's almost like molecular Lego for drug discovery," says Wu. "You can look at how the atoms fit, calculate how they're binding, and design better-targeted molecules."

More than looks

During his postdoctoral research, structural biologist Maofu Liao had to choose: specialize in tried-and-true x-ray crystallography or in the upstart, cryo-EM.

Liao chose cryo-EM.

"We think about proteins as molecular machines because in their native environment different parts move and do so repeatedly," says Liao, now an HMS assistant professor of cell biology. "But until cryo-EM, we mostly saw the details of proteins only in a fixed shape and conformation."

"We're not happy anymore with just seeing what a protein looks like," he adds.

Liao has been at the forefront of efforts to reveal the structures of dynamic proteins embedded in cell membranes, which are extraordinarily difficult to study with x-ray crystallography. These proteins exist in an ever-shifting sea of lipids—many are in constant motion; opening and closing during chemical transport; spinning like motors to generate energy, even, as in the case of the lipopolysaccharide flippase in bacteria, moving a large lipid molecule attached with chains of sugar to build protective walls around cells.

Using cryo-EM, however, Liao and colleagues have revealed exactly how these and other proteins carry out such remarkable feats.

"People have long said that structure is function," says Liao. "I think that was a more conceptual statement in the past, but will become more realistic in the coming years. I'm very optimistic about the future of cryo-EM, not because it will help us discover more new structures, but because it will allow us to directly visualize function."

It took decades before it became clear whether cryo-EM would ever be broadly useful.

The addition of cryo-EM to the structural biology toolbox has essentially opened a door to a new world of biological insight. But cryo-EM development is far from finished. An emerging technique known as cryo-electron tomography, something like an atomic-level CT scan, could soon allow researchers to study proteins in the cellular environment and not solely as isolated molecules in solution.

"It's clear that the field is headed toward studying the structure, organization, and interaction of molecules as they exist in their native environment, for example, determining the structures of ribosomes as they make a protein in a cell," Harrison says.

"But the key to structural biology," he adds, "has always been great biochemistry and sample preparation: Otherwise, you're imaging something meaningless. Many labs interested in structure are going to have to first relearn how to be biochemists."

Ever the visionary, Henderson, who knew decades ago that the promise of cryo-EM was just a technical issue or two from being realized, sees a bright future ahead.

"Cryo-EM is already the dominant technology in structural biology," Henderson says. "The goal now is to make it cheaper, faster, and more reliable, so that anybody can use it. I think it will someday become a common technique like measuring pH or sequencing DNA. It will only get more dominant."

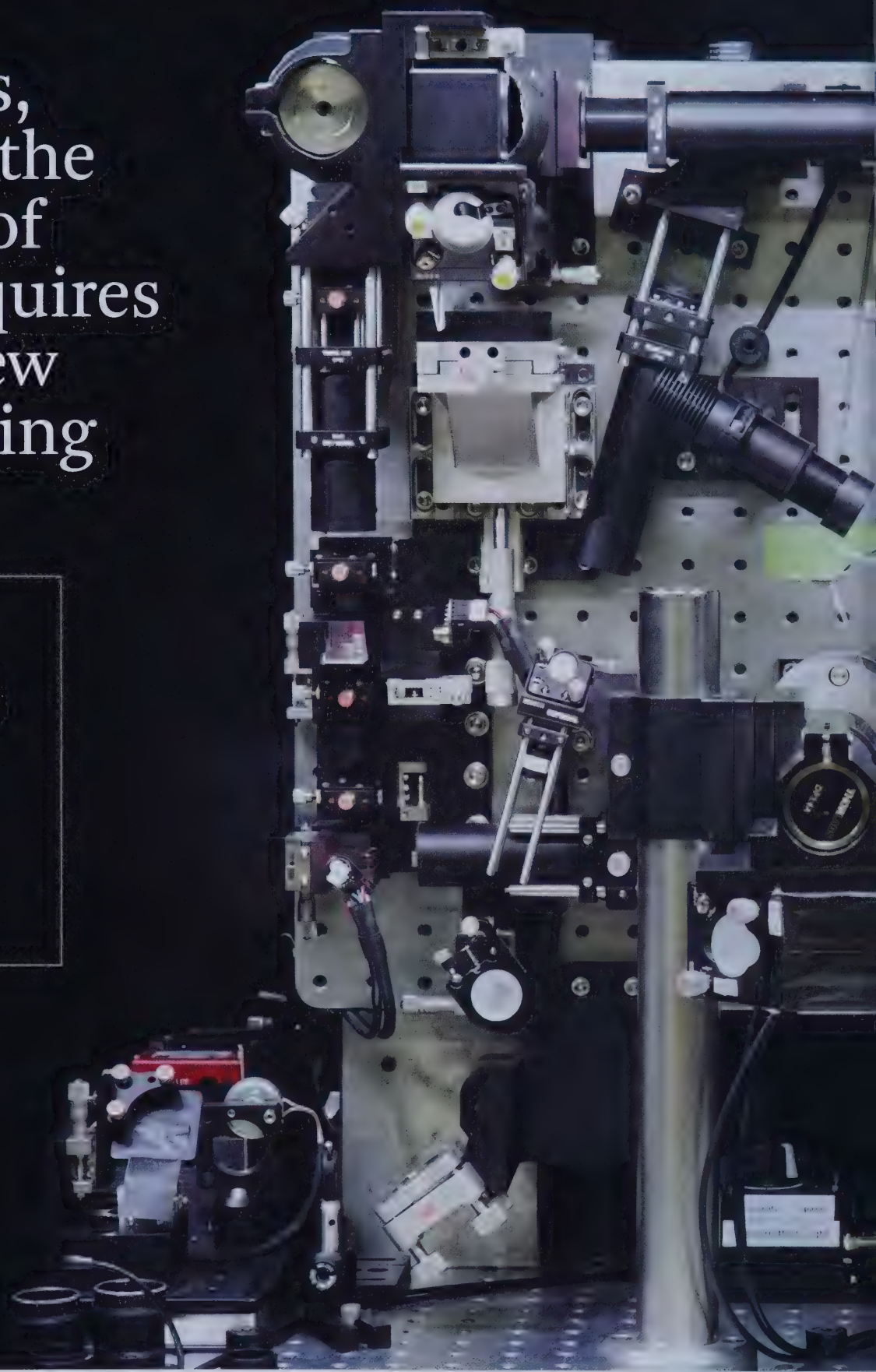
Kevin Jiang is a science writer in the HMS Office of Communications and External Relations.

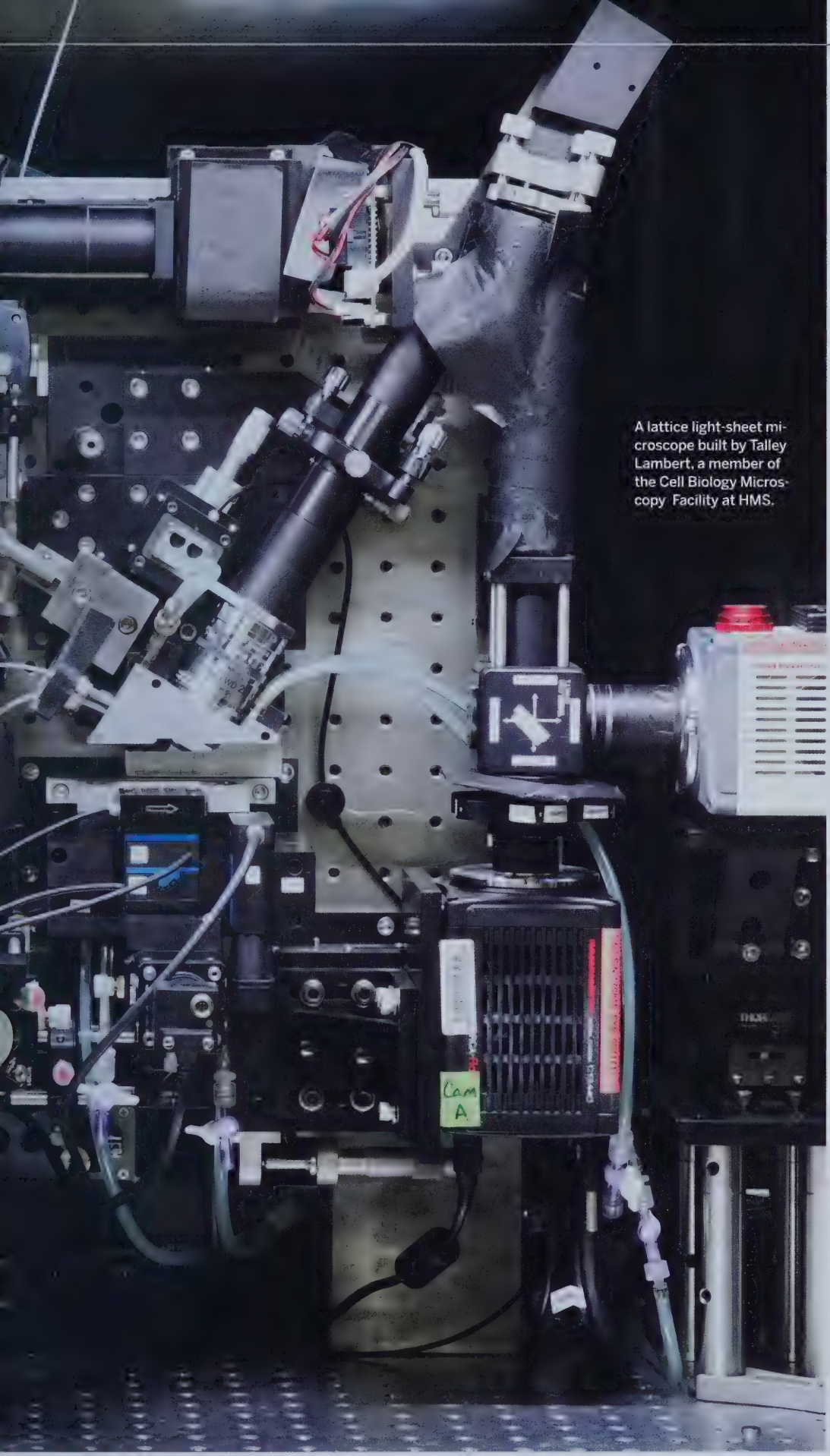
In 1960, during her first month as a medical officer of the U.S. Food and Drug Administration, Frances Kelsey (left) refused to allow thalidomide to be used in this country. She was concerned by data indicating dangerous side effects from the sedative. By 1961, reports of birth defects in thousands of children in Europe led to its removal from the market. Kelsey went on to help shape FDA rules that codify patient protections in drug investigations, including gaining informed consent and ensuring that a drug is safe and effective.

Sometimes, answering the questions of science requires creating new ways of seeing

Dream Machines

BY STEPHANIE DUTCHEN





A lattice light-sheet microscope built by Talley Lambert, a member of the Cell Biology Microscopy Facility at HMS.

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Bernardo Sabatini vowed that when he moved into his new office, he wouldn't clutter it with microscope parts.

The resolution didn't stick.

"This is a piece of a laser-scanning microscope I was building," he says of a black contraption beside a family photo on his bookshelf. The guts of other instruments litter his desk and windowsill.

Originally a biomedical engineer, Sabatini, MD '95, PhD '99, the Alice and Rodman W. Moorhead III Professor of Neurobiology at HMS, builds imaging devices because it's fun, because he hates having trainees expend their talent on labor-intensive tasks that more sophisticated equipment could do for them, and because he's frustrated by questions about the brain he can't answer with existing technologies. He's currently trying to stitch together three microscopes to get a broader picture of synaptic circuits.

"A lot of our ability to get data that other people don't have comes from our having built the hardware, designed the optics, and written the software," he says.

"Plus," he confesses, "I just love tinkering with stuff."

Over in cell biology, Tomas Kirchhausen admits to similar tendencies.

"I'm a borrower," says Kirchhausen, an HMS professor of cell biology and the Springer Family Chair of Pediatrics and senior investigator at Boston Children's Hospital. His inclination to find and modify imaging instruments that can better serve his science has made him one of the people deeply involved in importing the latest visualization devices to the Quad.

Faculty and staff across HMS are adapting, combining, optimizing, and designing new visualization technologies to solve problems in biology and medicine.

The fruits of their innovation range from microscopes to sample-preparation techniques to image processing and analysis.

Whether the components are tweaked or custom-made, excitement about the capabilities of modern optics is running high on campus as researchers and clinicians catch sight of phenomena they've been chasing for years, using the images and videos they capture to not only evaluate but also generate new hypotheses.

"Microscopes now can be used not just for passive observation but to induce changes in living tissue," says Aurélien Bègue, co-director of the Neurobiology Imaging Facility and an instructor in neurobiology at HMS. "You become an active player."

Imaging innovation convenes departments and institutions, which increasingly pool resources as devices require too much money or expertise to duplicate in every group. At the same time, many labs that innovate do so to bring down costs and provide the right balance of simplicity, flexibility, and effectiveness for users.

Innovation also arises from multidisciplinary collaborations and attracts people who blend traditional specialties. Such individuals tend to share a zeal for bricolage and for tackling problems, trying new things, remaining optimistic that solutions will eventually present themselves, and in the case of administrators, nurturing creativity in their labs.

The result: "We can look at life," says Kirchhausen. "Today is like the Renaissance, when people were exploring the world. Genomics, proteomics, transcriptomics, these are snapshots of composition. We can now bring cell dynamics into that. And that's exquisite. I wish I could live a hundred years longer."

The first time Santagata saw one of Agar's slides, he marveled at how clearly he could distinguish tumor from nontumor.

Fresh, not faded

Sandro Santagata, an HMS assistant professor of pathology at Brigham and Women's Hospital, has been collaborating with HMS faculty to explore the possibilities of new imaging technologies for pathologists and compare the findings to hematoxylin and eosin (H&E) stains—the purple- and pink-hued tissue slides that have formed the backbone of clinical diagnosis for more than a century.

Nathalie Agar, an HMS associate professor of neurosurgery and associate professor of radiology at Brigham and Women's, uses mass spectrometers to produce images that reveal incredible molecular heterogeneity within tumor samples. The first time Santagata saw one of Agar's slides, he marveled at how quickly and clearly he could distinguish tumor from nontumor.

"The molecules have always been there, but we've never detected them in this fashion or used them for these applications," he says. "You start to see the power of these techniques. There is a flood of molecular information, and we're just at the beginning of knowing what to do with it."

Meanwhile, Peter Sorger, the Otto Krayer Professor of Systems Pharmacology at HMS, wants to extract more information from cell cultures and patient tissue samples to better understand how different cells and individuals respond to drugs.

The typical method has been to use antibodies to attach fluorescent tags to molecules of interest. But since fluorophores usually come in only a few colors, ones that don't interfere with each other, most of the time researchers can study only two or three proteins in a given sample. That's no longer sufficient for those who seek a broader picture of cellular responses.

"To understand what's going on, you need to expand your capacity. You try to measure multiple things at a time," says Jia-Ren Lin, a research associate in therapeutic science in the Laboratory of Systems Pharmacology.

Lin relaxes by inventing things. He cobbled together a technique that allows researchers to apply fluorophores to three markers and snap microscopy images, then deactivate the tags in a chemical bath and apply three more—for up to twenty rounds and a total of sixty markers, depending on tissue fragility.

Software written and adapted by Sorger's group combines the layers and allows scientists to manipulate 3D digital reconstructions of their samples, turn markers on and off, and otherwise explore terabytes of biological information distilled into vibrant images.

"Genomics, proteomics, transcriptomics, these are snapshots of composition. We can now bring cell dynamics into that. That's exquisite."

Neurobiologist Bernardo Sabatini (left), cell biologist Tomas Kirchhausen (above), and systems pharmacologist Peter Sorger.

The team dubbed the method cyclic immunofluorescence, or CyCIF, and it has taken the HMS pathology community by storm since Sorger published the protocols, software, and initial results online for free in May 2018.

Commercial equivalents of CyCIF exist, but they're expensive, can't run as many cycles, and sometimes use proprietary antibodies, says Lin. By contrast, CyCIF can be performed with a few chemicals found at local pharmacies and hundreds of antibodies available on the market. It can be combined with whichever microscope a researcher has in her lab.

"Our having done this inhouse is not intended to prevent commercialization but to accelerate it," says Sorger. "The hope is we'll develop a clinically useful test so that when a patient comes in with brain cancer, somebody like Sandro can quickly generate a twenty-color image to diagnose them."

Santagata believes Sorger's and Agar's innovations are ushering in a long-awaited era of quantitative pathology.

"We can be very precise now with measuring the amounts of markers, the numbers and densities of cells, and the relationships of cells to one another, which we were never able to do with immunohistochemistry," he says.

This year, Santagata co-authored a case study with Sorger, Lin, and neuro-oncologist David Reardon at Dana-Farber Cancer Institute, in which they reported using CyCIF to measure immune cell distribution and signaling in a patient whose rare brain tumor kept returning despite multiple surgeries and experimental treatments. The images indicated a specific immunotherapy would work.

The patient is now in remission.

Basic science applications are equally promising. Sorger is eager to explore the relationships among tumor, microenvironment, and immune invasion, while Santagata thrills at the amount of tissue now available for analysis: CyCIF can be run on top of H&E, even on decades-old samples.

"Nobody had ever seen pictures at that resolution," Sorger says of the first time they

Hematoxylin is a dye extracted from the logwood tree, *Haematoxylon campechianum*. Used by native Caribbean populations well before the Spanish wrote of it in the

1500s,

its oxidized form, hematein, is thought to have been first used in histology in the

1830s.

Hematoxylin was used to dye U.S. soldiers' uniforms during the Civil War and World Wars I and II, and it is still used to dye surgical sutures and silk.

Members of the Neurobiology Imaging Facility (left to right): Aurélien Bègue, Michelle Ocaña, and Mahmoud El-Rifai.

JOHN SOARES

performed CyCIF on an archival breast biopsy. "Nobody even knew data existed at that resolution."

Road trip

For decades, Kirchhausen had built world-leading expertise in the mechanics of how cells envelop incoming viruses, bacteria, and toxins in vesicles coated with the protein clathrin. He determined the atomic structure of clathrin. He peered at the process, called clathrin-mediated endocytosis, through the best microscopes available. He partnered with animators, sculptors, and musicians to creatively interpret the steps involved in its mechanism of action. He laid the foundation for a compound used today to block endocytosis. But even the most advanced technologies left a lot to the imagination.

Then Kirchhausen viewed his lifelong interest through a lattice light-sheet microscope.

"Oh, my God," he recalls. "I could see all the little guys, the viruses, going in. I could see every single event in real time throughout the whole surface of a cell. Seeing that had been a dream of mine for I don't know how many years."

Light-sheet microscopes debuted in the 1990s as a solution to photobleaching in live cell samples. Other microscopes illuminate the entire sample while the lens captures one plane of tissue at a time; by the time a researcher reaches the last plane, the sample has lost quality from extended illumination. Light-sheet microscopes emit a microns-thin sheet of laser light that illuminates only the plane being imaged, keeping exposure times short and prolonging sample freshness as the tissue sweeps through the lens' line of sight. The sweep repeats at intervals for hours or days. The planes are then computationally combined into a 3D movie that shows what's happening in the cells over time.

"I think light-sheet is the most exciting thing going on in optical microscopy right now," says Talley Lambert, a research associate in cell biology and manager of the Cell Biology Microscopy Facility at HMS. "Anybody doing live imaging of single cells or small chunks of cells has something to gain from this technology."

Several iterations of light-sheet microscopes have appeared in recent years. The lattice light-sheet microscope was devised in 2014 by Howard Hughes Medical Institute (HHMI) investigator Eric Betzig, who

won the Nobel Prize in Chemistry that year for co-inventing super-resolution microscopy. The lattice employs intricate math and physics to produce a thinner light sheet without shrinking the length of the plane, making it especially useful for subcellular imaging. Kirchhausen's group built one at HHMI's Janelia Research Campus under Betzig's guidance and drove it to Boston. One year later, in 2015, six HMS basic science departments contributed to purchasing the parts for a second, which Lambert helped build.

Kirchhausen uses his lattice light-sheet to uncover details about endocytosis, viral entry, and cell division that have eluded observation until now.

"I thought I was an expert. Turns out, when we repeat an experiment using what we think are the same conditions—whoops, there's something new, some surprise."

Still, he remains thirsty for improvement. Earlier this year, Kirchhausen's group worked with Betzig's to enhance lattice light-sheet with adaptive optics, a technique developed by astronomers to sharpen images of the cosmos taken from Earth's surface. In a telescope, a laser beam creates a false star—a control—so computers can correct for atmospheric distortions and make celestial objects appear more clearly. Similarly, a laser added to the lattice light-sheet allows researchers to "de-fuzz" their area of interest by compensating for the cellular material that lies between it and the lens.

"Now the revolution is complete," says Kirchhausen. "We can not only see cells with close to single-molecule detail, but we can do the same in a cluster of cells. We can look at cells in their natural environment."

Srigokul Upadhyayula, an HMS instructor in pediatrics working in the Kirchhausen lab, is building an adaptive optics microscope that is a complete redesign of the one at HHMI. It will combine the functionality of several instruments, including super-resolution and two-photon microscopy, to form a sort of Swiss Army knife mega-microscope that can capture an immense range of temporal and spatial resolutions during a single experiment.

Upadhyayula, who is also a member of a team overseen by Betzig, continually evolves Kirchhausen's lattice light-sheet to make it more capable, compact, user-friendly, and economical without sacrificing quality. Always, the modifications address roadblocks that arise during research.

"I'm an engineer at heart. I always grow when I'm trying to solve a problem," he says.

Light captivates Upadhyayula. He began his PhD studying solar energy and then turned to biological imaging, fascinated by modern microscopes' ability to manipulate light. Now he helps his collaborators answer the question: When can you believe what you see?

Understanding how light interacts with each lens and mirror helps him build and calibrate today's exceptionally complicated microscopes, which in turn gives him a deep appreciation for the instruments' limitations.

"Operating a microscope is not just about knowing which button to push," says Bègue of the Neurobiology Imaging core. "We're getting to a point where the science we're trying to do is not so simple. You need a good grasp of how these microscopes operate in order to do cutting-edge experiments. And you need to know your optics in order not to make mistakes: It is easy to treat an image the wrong way. In order to do good science, you need to apply the same rigor to microscopy and image processing that you do to statistical analysis."

Now he helps his collaborators answer the question: When can you believe what you see?

Swept away

There are alternatives to adaptive optics for handling soft-tissue distortion: You can also simply remove unneeded tissue.

Consider the brain. Like a gelatin salad swirled with whipped cream and fruit, it's filled with fats and other molecules that scatter light rays before they can reach a microscope lens, says Michelle Ocaña, co-director of the Neurobiology Imaging Facility and a senior imaging specialist at HMS.

A set of techniques known as tissue clearing wash away or bleach these inclusions and leave the natural protein scaffolding in place. The result: a whole, transparent organ with key structures intact. Researchers then add stains or use genetically expressed fluorescence to study structures of interest without anything in the way.

In late 2017, Ocaña's group started offering tissue clearing to the Quad. Requests streamed in. So far, the team has helped researchers clear rat brains as well as mouse brains, jaws, prostates, kidneys, intestines, and spinal cords before imaging them with a simple light-sheet microscope.

"It's booming. My feeling is, whatever you want to clear, let's try," says Mahmoud El-Rifai, a technician in the facility who specializes in tissue clearing and array tomography.

The biggest challenge yet arrived this summer when a postdoctoral fellow in the lab of Wade Regehr, an HMS professor of neurobiology, wanted to investigate whether the meninges enclosing a rodent brain contain axons and neurons. Previous attempts had failed because the delicate membranes tore whenever researchers removed the skull to observe them.

El-Rifai thought, why not try clearing the whole skull and brain together? That way

"The good thing is I have physics on my side. We have centuries of knowledge about light. You know it's eventually going to work because physics says it will."

"you don't have to peel anything; everything remains intact," he says. No one had done that before, but he thought it would be worth the attempt.

"The results were unbelievable," he says. "Everything became so clear you couldn't recognize it. We stained the brain and got some nice images, and the researchers saw what they needed to see."

El-Rifai believes his inclination to embrace the unfamiliar and take risks arises from both the lab culture and his personal history.

When his family moved to the United States from Lebanon in 2010, El-Rifai was 18 years old and spoke no English. He started taking language classes, got a night job in a bakery, and put himself through college, graduating in four years with a degree in biomedical engineering.

"It was exhausting," he admits, "but my thought was: work hard and you'll find something at the end. You've got to keep trying, because nothing will work for you the first time."

His philosophy applies to array tomography as well, the painstaking technique he swiftly mastered. Whereas tissue clearing works best on a large scale, array tomography, invented in 2007, provides high-resolution 3D images at the molecular level: "Where the secrets are," says El-Rifai.

After a tissue sample is fixed and embedded in plastic, El-Rifai slices it into 70-nanometer sections, each attached to the next and lined up on a slide. It can take a year to section one axon. Imaging the sections one by one ensures that each receives the same amount of stain and light. Then the images are stacked via software, producing terabytes of data.

Not content with becoming an expert in new and difficult imaging technologies, El-Rifai alters them to meet people's needs. He modified array tomography protocols to accommodate a zebrafish researcher's hydrophobic resin and is helping another colleague experiment with staining RNAs instead of proteins. After discovering that many researchers choose one particular tissue-clearing technique because it has a lot of documentation about supported antibodies, he began compiling a similar database for a less popular but equally valuable technique. He hopes it will help people select the method that's best suited to their projects.

Colleagues have come asking for super-resolution microscopy only to have Lambert discover that confocal could do the job with some fine-tuning.

A little to the left

It's dark in the cell biology microscopy room. Fans from cooling units and computers provide a steady background hum as Lambert focuses on a sample—in this case, a fluorescent bead on a glass slide.

Lambert snaps a picture with the instrument, which resembles an elaborate erector set more than a traditional microscope. The image of the bead is a little blurry. He adjusts a knob and takes another photo: still not quite right. He tweaks a different knob: better, but room for improvement. He swaps out a lens and tries again. He's so engrossed he doesn't notice his colleagues coming and going.

Lambert doesn't care about the bead itself. Rather, he's intent on pushing the microscope to its full potential.

"I love tinkering on the microscopes," he says. "I love making a more beautiful point spread function," the image of an infinitely small dot. The cleaner he can make it, the better his microscope is performing.

"A lot of labs are microscope builders," he says. "I am a microscope optimizer.

"People who design new ones, they drop it when they're done and go on to the next one. I am more than happy to pick it up and evaluate whether it is truly useful. If it is, I will put a lot of time and effort into optimizing and democratizing that technology."

As part of a core facility team assembled by Jennifer Waters, director of microscopy and an HMS lecturer on cell biology, Lambert has tackled recent microscopes including super-resolution, structured illumination, and several kinds of light-sheets. Yet, it's just as important to him to improve upon existing technologies as it is to introduce new instruments to the Quad.

While some novelties, like light-sheet, fill a niche, he says, some older technologies remain underexploited, sometimes without researchers' awareness. Colleagues have come to the core asking for super-resolution microscopy only to have Lambert discover that confocal could do the job with some fine-tuning.

"We need to better use what has been developed," he says. "That's sometimes not as exciting as designing a whole new technique, but it's more far-reaching, and it's far cheaper. Optimization definitely should come before innovation."

Lambert began his career as a neurobiologist, studying learning and memory and synaptic morphology, until, as a postdoctoral fellow, he realized he enjoyed methodology more. His foundation in biology helps him meet collaborators in the middle, discussing their research goals in enough detail that he can advise on the best technology for the job.

In the neurobiology core, Bègue credits his own background in pharmacy and neuroscience, which he studied in addition to math and engineering, for allowing him to understand colleagues' needs well enough to build solutions for them. He derives similar satisfaction from helping.

"The results were unbelievable. Everything became so clear you couldn't recognize it. We stained the brain, and the researchers saw what they needed to see."

"One thing I regret as a biologist is that I don't have a lot of questions that keep me up at night," he says. "But when I meet other scientists and I can say, 'We're going to find a way to help you with that question that has been haunting you for the past ten years,' that's very satisfying to me."

Even as they recognize the value in centralizing expertise, Bègue and Lambert share a passion for making imaging technology more accessible. Lambert writes software, designs graphical user interfaces, authors review articles, simplifies tools, and lowers costs, while Bègue plans to organize basic optics seminars and host in-depth consultations with Quad labs to discuss their imaging challenges.

Tinkering with microscopes provides plenty of experience in overcoming such challenges.

"Problem solving is great, but it means you're always dealing with a problem," says Bègue, who builds and modifies devices for himself and others. "You will try many solutions and 99.999 percent of them will fail. Not everyone is built to handle that much frustration."

Rather than throwing his equipment, or himself, against the wall, Bègue starts by throwing every idea he can think of at a problem, tries to learn from each failure, and waits for small successes he can build upon. He also breaks down complex challenges into smaller components.

"Someone will say, 'We want a microscope that will do *x*, *y*, and *z*, and make coffee too,'" he quips. "I start by trying to do *x*. If that works, I'll see if I can add *y* to it."

Bègue draws confidence from the fundamental laws governing optics. "The good thing is I have physics on my side," he says. "We have centuries of knowledge about light. You know it's eventually going to work because physics says it will."

The downside is that if nothing works, he knows he's the one to blame. "With biology, you can say, oh, maybe my mouse behaved differently today. Well, light does not decide to do something different."

Lambert, too, knows the pain of beating at a problem for days and then, "if you're lucky, you have a microcosm of a eureka moment that improves that teeny process." The joy lies in "figuring stuff out."

Best laid plans

Like many neurobiologists, Sabatini wants to move from studying single neurons or small clusters to observing thousands of neurons at once, catching in action the circuits that underlie behavior.

He has already advanced the field through innovations in optogenetics, a technology that activates desired neurons with light, and two-photon microscopy, a high-resolution 3D fluorescence imaging technique. Earlier this year, his lab created peptides that photoactivate so researchers can study the function of natural opioids produced by the brain. But there's a long way to go.

Right now, he says, he's completing "a beast of an instrument" that should help with several burning questions. The first part contains the same beam-emitting device found in lattice light-sheet microscopes, which Sabatini uses to swiftly map all the neurons in a tissue sample. The second part is a holographic optogenetic stimulation microscope, which lets Sabatini create 3D patterns of light that activate whichever presynaptic neurons he wants. He can then record the downstream effects in postsynaptic neurons using the third component, invented by an MIT colleague: a two-photon microscope combined with an electrode-implanting robot.

Sabatini wants to move from studying single neurons or small clusters to observing thousands of neurons at once.

The as-yet-unnamed behemoth is limited to five or ten electrodes at a time, but from those, Sabatini expects to be able to infer the activity of hundreds to thousands of neurons per experiment. He's itching to illuminate a "really cool" type of neuron his lab discovered that releases multiple, seemingly contradictory, neurotransmitters; other instruments haven't found the chemicals' targets nor revealed why they simultaneously excite and inhibit. He's also keen to investigate whether another class of neurons changes the ratio of neurotransmitters released when an animal experiences something new, teaching it to seek similarly good, or avoid similarly bad, experiences in the future.

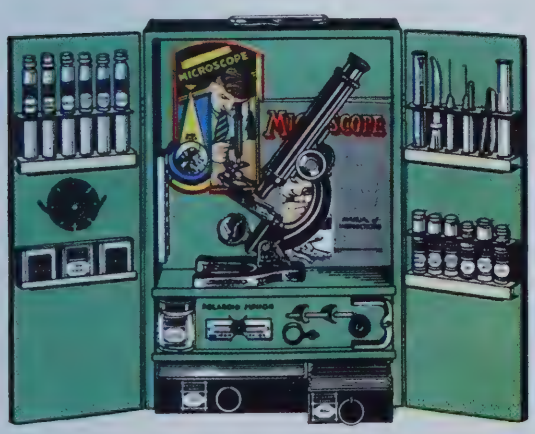
When those projects get underway, he plans to build a second version of the microscope to help a cross-institutional team at HMS, the Broad Institute of MIT and Harvard, and the Harvard Stem Cell Institute analyze how genetic variation changes functional neurocircuitry in brain organoids. Additional colleagues wait in the wings.

"There are a lot of problems waiting for this machine," says Sabatini.

He just needs to get the pesky optics aligned first.

Then it will be on to troubleshooting software issues—and preparing to create whatever instrument their research demands next. HM

Stephanie Dutchen is a science writer in the HMS Office of Communications and External Relations.



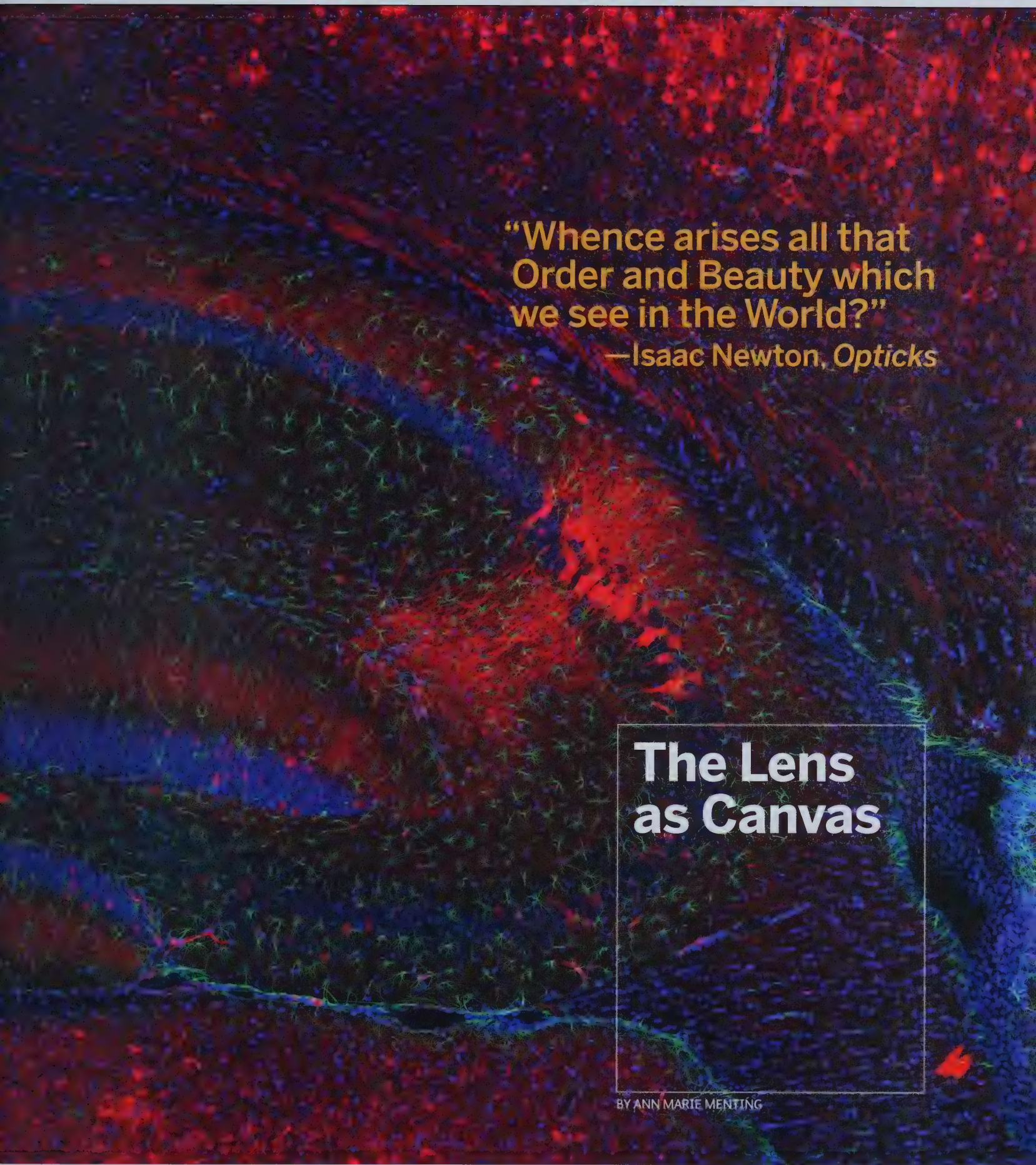
No. 7 MICROSCOPE SET

The Connecticut-based A.C. Gilbert Company, which began in 1906 as the Mysto Manufacturing Company, produced a range of educational toys. Its microscope sets, one of which (left) appears in an Eli Whitney Museum catalog of Gilbert toys, debuted in 1934.

Gilbert was a Yale medical school graduate who paid for his medical education with proceeds from his work as a magician. He is best known, however, for his science-based toys, which included the Erector set. Aside from entertaining children for years, Erector sets have also captivated adults: In 1949, a set was used by physicians at Yale School of Medicine to model an early artificial heart.

The hippocampus, a brain region important for learning and memory, was captured by David Brann, PhD 2022, a graduate student in the lab of neurobiologist Sandeep Robert (Bob) Datta, MD '97, PhD '04. This image shows the use of a new adeno-associated viral vector, called PHP.eB, capable of transducing neurons in a wide range of areas.

"The density of astrocytes (green) reminds us to also consider the role of non-neuronal supportive cells in modulating neuronal activity and in hippocampal-dependent learning," says Brann. "I was surprised at the amount of labeling by the PHP.eB vector in the hippocampal CA2 region (cells in red in the center). Although most studies of hippocampal learning and function neglect the CA2 region, recent work suggests that it may play a crucial role in social memory."

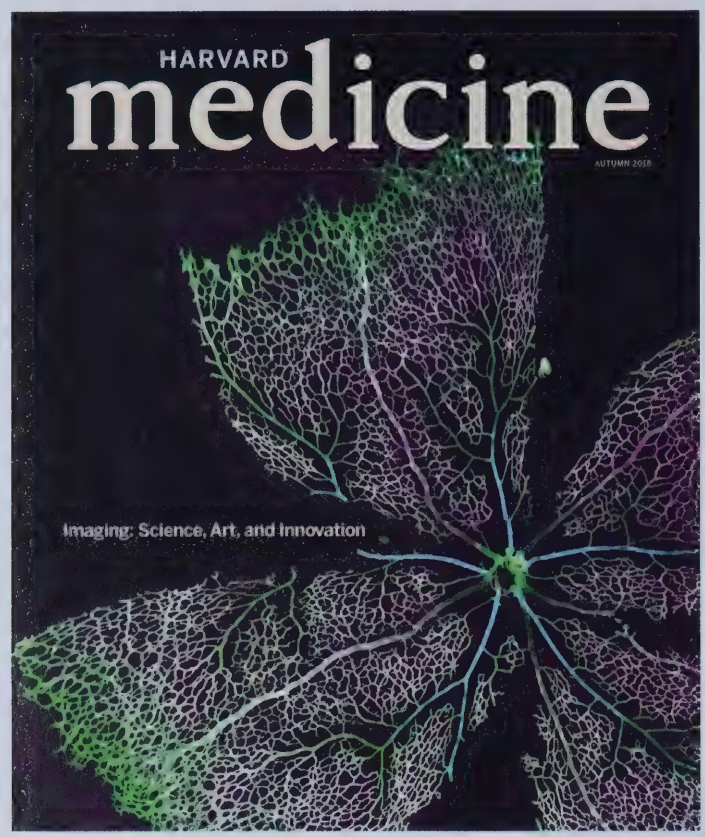


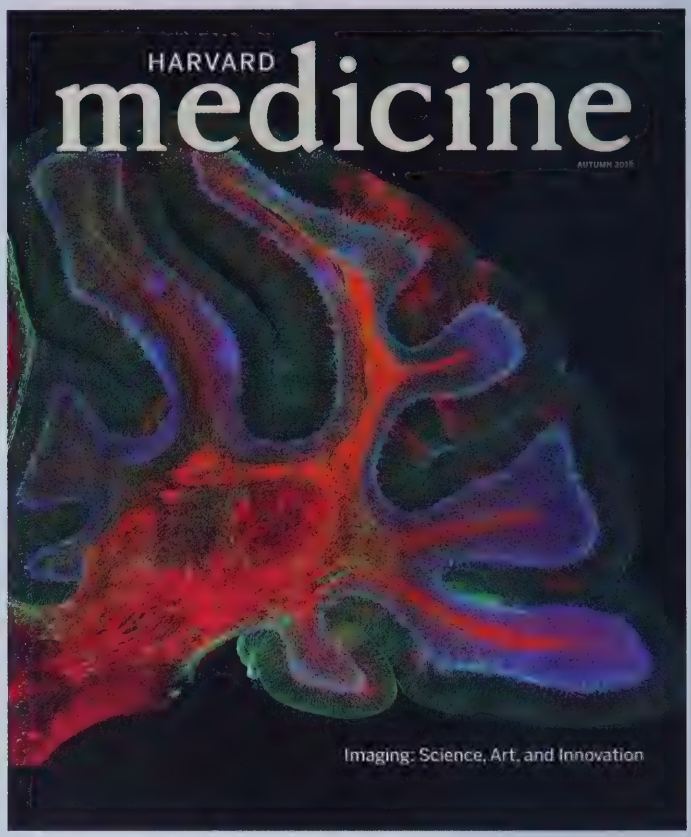
"Whence arises all that Order and Beauty which we see in the World?"

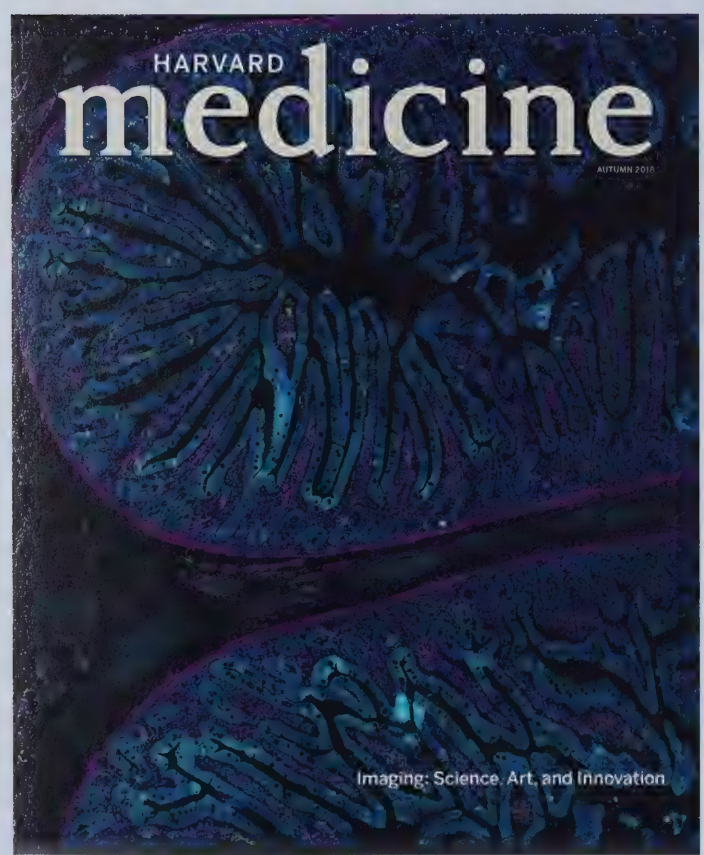
—Isaac Newton, *Opticks*

The Lens as Canvas

BY ANN MARIE MENTING







Beauty Unseen, a photo contest held this spring for researchers on the HMS Quad, garnered a number of stunning images of the microscopic worlds studied by the School's faculty, trainees, and students, including all the images in this essay.

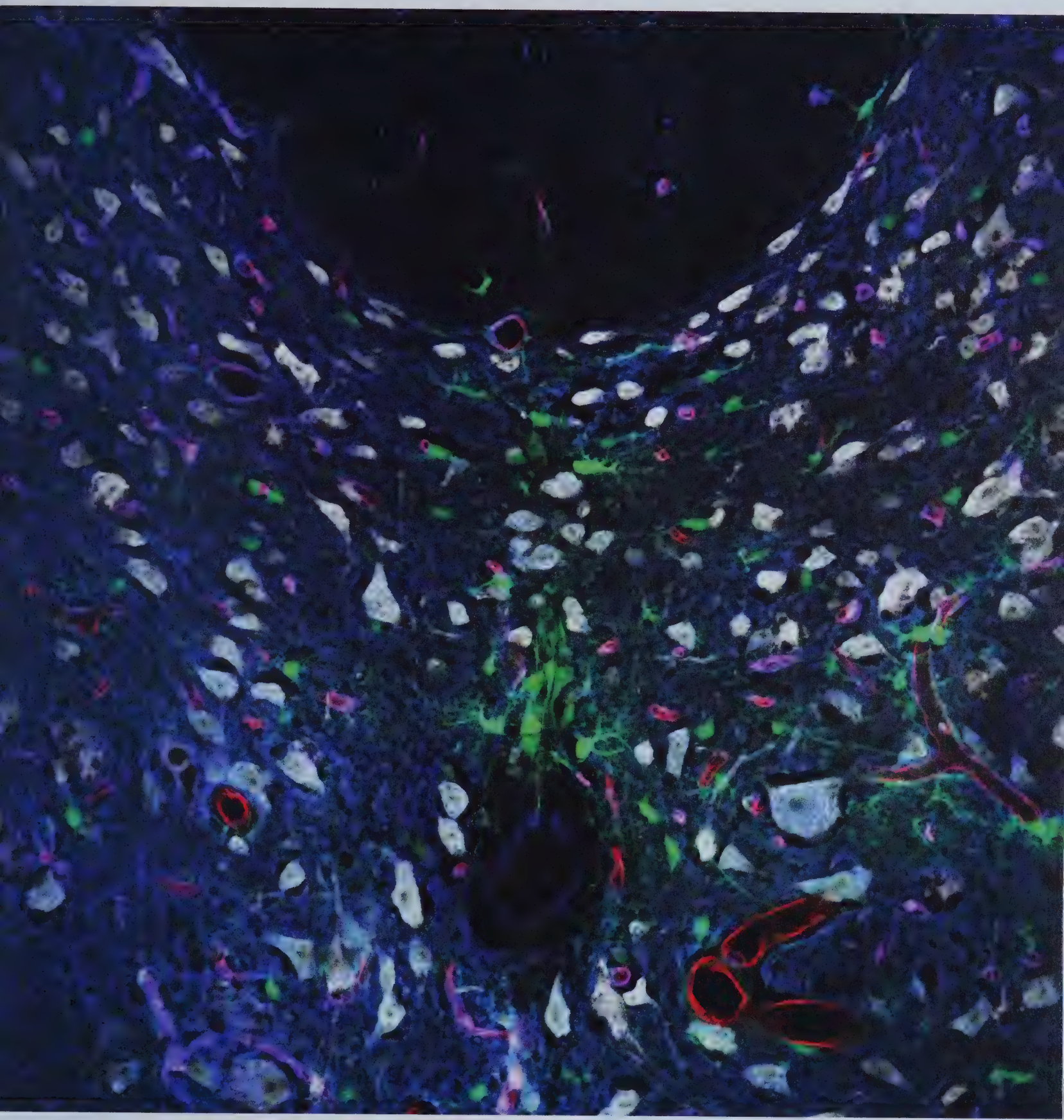
The three covers shown here, celebrating the images of the first-, second-, and third-place contest winners, were developed and printed for this issue of *Harvard Medicine* and distributed randomly to our readers.

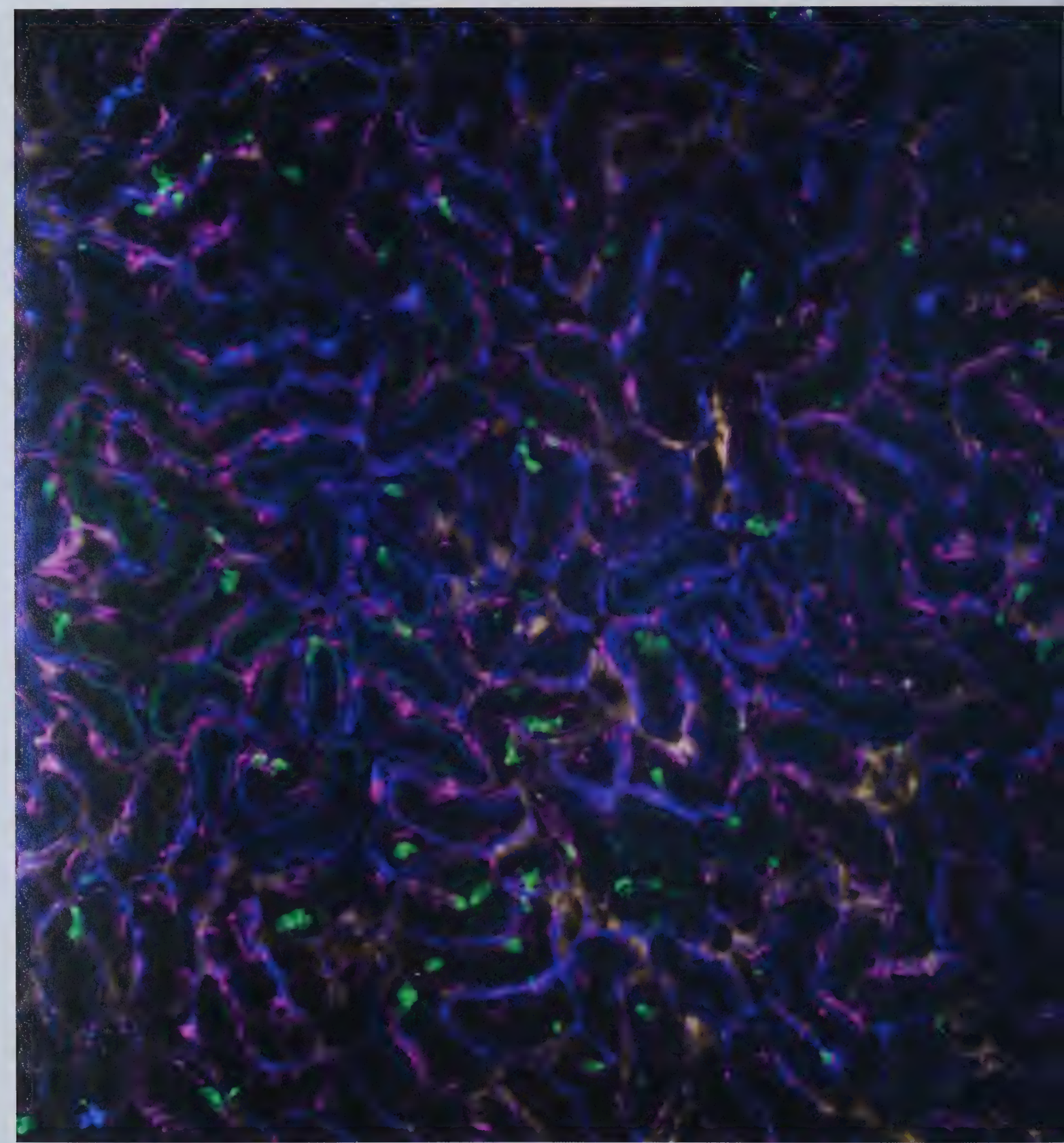
Brian Chow submitted the image that captured the top prize (above, left). Chow, a graduate student in the laboratory of neurobiologist Chenghua Gu, photographed the blood-retinal barrier in a mouse. By visualizing how the retina is vascularized, he hopes to better understand how this barrier nourishes and protects the retina.

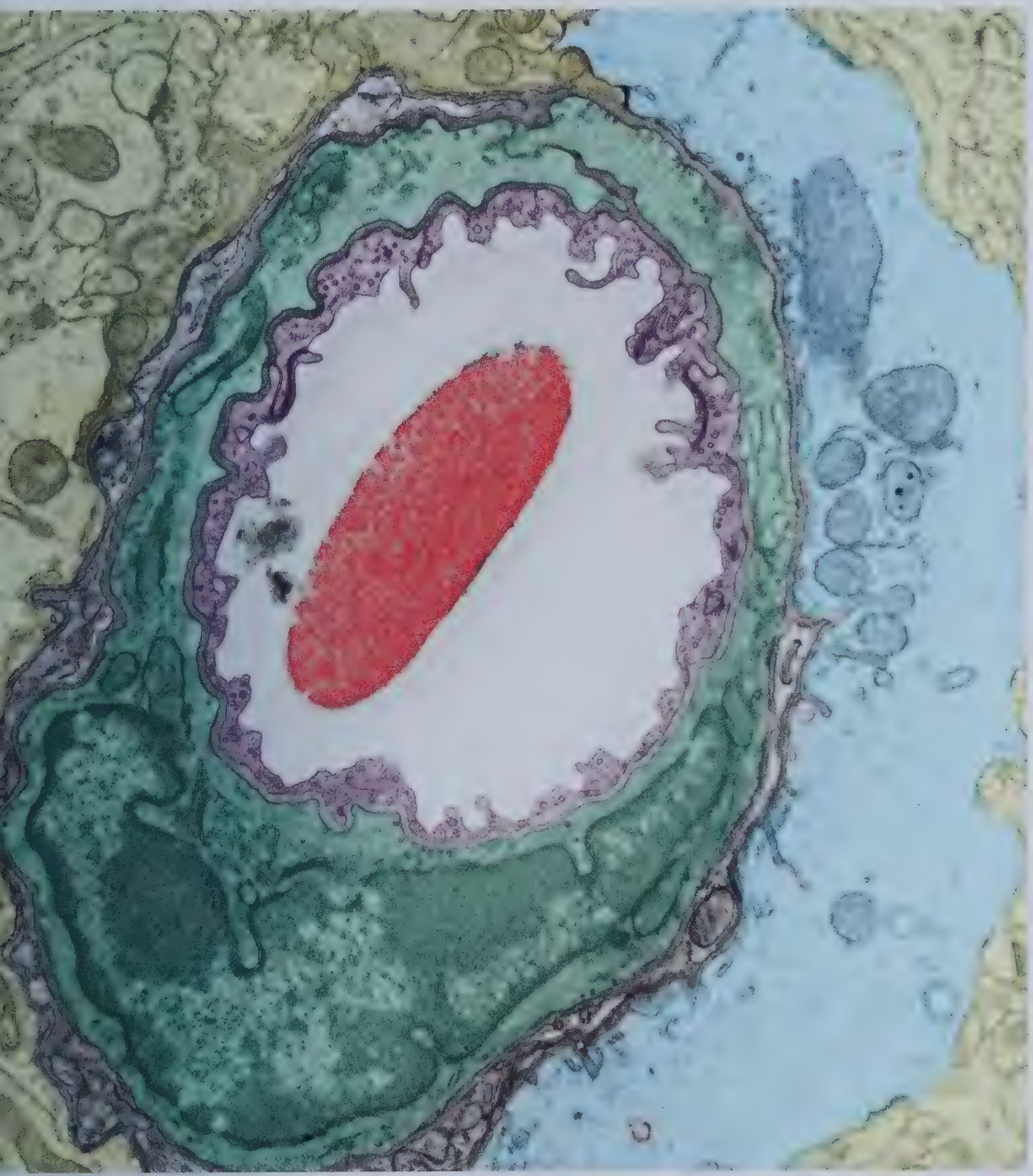
David Brann, PhD 2022, in Sandeep Datta's neurobiology group, took second place with his image of a section of the brain's cerebellum (above). He seeks to investigate brain functions by refining the tools used to visualize, monitor, and modulate cells across the central nervous system.

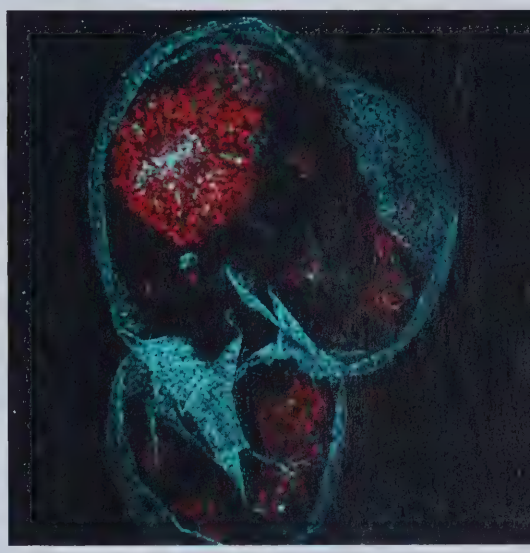
Zoltan Maliga's image (left) was awarded third place. Maliga, MMS '99, PhD '04, a senior research scientist with Peter Sorger in the Laboratory of Systems Pharmacology, is interested in the architecture of tissues and the mechanisms that lead to disease. His image of the human small intestine was processed with a novel method called cyclic immunofluorescence. The method, developed at HMS, allows scientists to characterize up to sixty markers in a single sample.

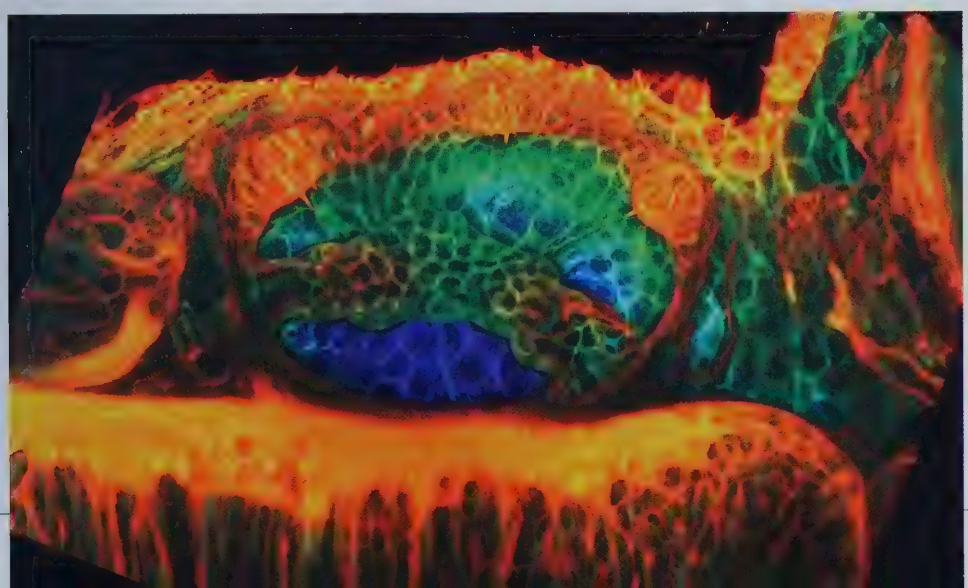
The image from Isle Bastille, PhD 2022, a graduate student in Gu's neurobiology lab (right), shows the central canal of the spinal cord (the cord is the dark oval at bottom center) and the surrounding gray matter. Bastille used two markers to delineate astrocytes, a type of support cell in the central nervous system, and their fine processes. This image was the first that allowed Bastille to clearly resolve astrocyte cell bodies, showing how their processes (blue) extend and wrap around blood vessels (red), often wedging themselves between blood vessels and neurons. Bastille says this research aims to decipher how spinal cord neurons receive nutrients and other molecules from the bloodstream, knowledge that is crucial to understanding spinal cord diseases.











In his image of an uninjured kidney in a live mouse (far left), Pei Xiong Liew, an HMS research fellow in the laboratory of pathologist Tanya Mayadas at Brigham and Women's Hospital, shows immune cells (green) traversing a bed of blood capillaries, which are lined with endothelial cells (blue); endothelial junctions are highlighted in magenta. In kidney disease, renal tubules (dark green) are disrupted, resulting in the recruitment of immune cells through the capillaries. By imaging how immune cells interact in host tissues in real time, Liew hopes to develop better treatments for patients with end-stage kidney disease.

Brian Chow in Chenghua Gu's neurobiology lab used electron microscopy to visualize the subcellular structures of a mouse brain artery (left, above). When arteries dilate, more blood can flow into the brain, helping to satisfy that organ's high metabolic demands.

In work characterizing a multiprotein complex that plays a role in protecting cells from viral infections, Philipp Merkl, a research fellow in the laboratory of microbiologist David Knipe, captured the nucleus of a human fibroblast cell (above), staining it to show the nuclear lamina, a dense fibrillar network coating the inside of the nuclear membrane (blue-green), and areas of viral replication (red). Within the areas of replication are additional filamentous structures (blue-green). These structures represent an assembly of several proteins on the viral DNA, including a protein of the nuclear lamina.

Akankshi Munjal's image of the inner ear of a zebrafish embryo (left, below) is part of her research on how the ear's semicircular canals form from simple tissue. A postdoc in the laboratory of geneticist Sean Megason, PhD '01, Munjal seeks to infer the forces required to shape organs by analyzing cell shapes.

In 1854, John Snow's field research led to this map depicting the clusters of cholera cases in the epidemic in London that year. His study of the pattern of the disease's occurrence led to the identification of the Broad Street pump as the source of the outbreak and provided evidence that cholera is a waterborne illness.

WIKIMEDIA/PUBLIC DOMAIN/MATTIAS PALUDI

Mapmaking is showing that geography may rival genetics as an indicator of human health

The Lay of the Land

BY JAKE MILLER

"There is something fundamental about a map," writes *New York Times* journalist John Noble Wilford in *The Mapmakers*, a history of cartography. Maps can excite the imagination, instill a desire to explore, and distill the physical connections between people, places, and things.

In various forms, maps have been in use for more than 5,000 years. Indigenous peoples of the Pacific islands used stick charts to navigate their way across the vast waters; early Inuit people carved detailed representations of their home coastlines from wood; and the Incas made clay and stone relief maps of their mountainous empire.

Today, vast quantities of data from satellite imagery, drone photos, and an increasing array of sensors are aggregated and tied to geographic coordinates that can be mapped and analyzed visually. Recent advances make it relatively simple to animate series to show how data move across a mapped region over time.

For researchers, population health workers, and clinicians, maps have become critical tools for analyzing data and communicating the results of that analysis to key audiences: policymakers, the public, and other researchers. This is especially important because so many risk factors for both infectious and noncommunicable diseases are tied to specific places. Where you are and where you have been play important roles in whether you get sick or stay well. Fortunately, digital cartography, remote sensing, social media, mobile communications, and other technological advances have made it increasingly feasible to develop maps that can be used in efforts to fight epidemics and promote well-being in real time.

On the dot

A cascade of red dots representing reported cases of tuberculosis seems to spill off the edge of a map of neighborhoods in Carabayllo, a municipality in Greater Lima, Peru. The community has developed so fast it has outgrown the census blocks that were meant to define it.

The map doesn't just show the fast pace of urban growth in Peru. It illustrates the importance of having a high-resolution visual of the geography of tuberculosis. The map shows percentages of households with the disease. Some census blocks are lightly shaded, indicating relatively few cases, while others are saturated with color. In those

areas, the incidence of the disease is five times greater than the national rate.

In Carabayllo, a team led by HMS researchers and Peruvian collaborators has begun a new project to use mapping technologies to target tuberculosis-eradication efforts as precisely as possible and to help build community engagement and participation.

"We have to think of tuberculosis epidemics as local," says Mercedes Becerra, an HMS professor of global health and social medicine and one of the leaders of the Carabayllo initiative. Becerra, along with Salmaan Keshavjee, PhD '98, an HMS professor of global health and social medicine, is a founder of the Zero TB Initiative, an international collaborative working with local coalitions to test and refine comprehensive treatment and prevention protocols to rapidly drive down tuberculosis rates.

The goal of the initiative is to create "islands of elimination," geographically defined regions within which no tuberculosis deaths or cases occur. Some of the initiative's collaborating sites will be on actual islands, others in discrete regions within cities. The initiative is infused with the importance of geography; it uses language that emphasizes location and focuses outreach on communal social spaces where many people at high risk of tuberculosis infection are likely to meet.

The Zero TB Initiative in Peru involves clinicians and researchers from HMS, Brigham and Women's Hospital, Partners In Health, and a number of Peru's community and government organizations at the local, municipal, and national levels.

Meredith Brooks, an HMS research fellow in global health and social medicine, is working with Becerra to create maps that combine data from municipal and federal records and from a local epidemiologic study conducted from 2009 through 2012 by a team led by Becerra and Megan Murray, MD '90, the Ronda Stryker and William Johnston Professor of Global Health at HMS. The study gathered information about social, economic, and environmental factors in homes affected by tuberculosis.

The goal is to create "islands of elimination," geographically defined regions within which no TB deaths or cases occur.

Mercedes Becerra

Brooks's maps are scaled at the neighborhood level and will be used to guide an intensive effort to search for, treat, and prevent tuberculosis in the hardest-hit parts of Carabayllo.

"The goal is to do more than make nice maps that show what happened with the epidemic historically," Brooks says. "We want to learn to use these data in real time, so we can respond to the disease where it's happening now."

The researchers plan to use maps in outreach efforts with community coalitions

"We want to learn to use these data in real time, so we can respond to the disease where it's happening now."

to illustrate the strength of the tuberculosis epidemic in specific zones and to highlight the local availability of treatment and prevention services.

Well, well, well

Although maps have been around for millennia, what we might recognize as data maps appeared comparatively recently. Edward Tufte, a statistician and well-known analyst and theorist on the presentation of data in visually comprehensible formats, notes that certain methods of displaying quantitative evidence are better than others: Good graphics are more likely to produce credible and precise findings and are more efficient than most other means of conveying data. He notes that a single data-rich map is capable of wrangling millions of bits of information into one easily deciphered display.

"No other method for the display of statistical information is so powerful," Tufte writes.

How powerful can be seen in the medical data map in *On the Mode of Communication of Cholera*, published in 1854 by John Snow, an English physician whose work is considered to be foundational to epidemiology. In his map, Snow overlays locations of cholera deaths and locations of public water pumps on a street map of Soho, then a suburb of London.

At the time, it was thought that cholera was transmitted by tainted air, but Snow suspected that the disease flowed from contaminated water. To gather data to either support or refute his notion, Snow went door to door to the homes of the deceased and asked surviving relatives where they obtained their water. All responses implicated the pump on Broad Street. The data Snow gathered also showed that neighbors who remained healthy got their drinking water elsewhere. The map he produced became both a tool for analysis—a way to look for patterns in the data—and a means of communicating his results: cholera was transmitted in water, and people could avoid contracting the disease if they did not draw their water from the contaminated pump.

Reproducing Snow's legwork and hand-drawn maps today would be prohibitively slow, when epidemics can be spread in hours by international travelers, and unwieldy for studying complex, multifactorial epidemics. In the past few decades, however, advances in information technology and the invention of digital cartography, including work done at the Harvard School of Design's Laboratory for Computer Graphics and Spatial Analysis, have transformed the field. A researcher at a computer, writes journalist Wilford, can, with a few clicks of a computer mouse, generate a map that not long ago would have taken a professional cartographer an entire career to create.

Our town

A pale yellow mantid sits with its long forelimbs bent as if in prayer, as still in death as it often was in life. Pinned to a board within a framed display that also includes beetles, saw-wasps, dragonflies, and other insect specimens, the mantid hangs on the wall of John Brownstein's office in Boston Children's Hospital's innovation lab. Each insect is labeled with its genus and species along with the location in Kenya where it was collected.

Brownstein, who leads a team that has charted new territory in the use of maps for biomedical research, for public health surveillance, and for guidance in clinical medicine, collected the creatures himself. Early in his career, he had an interest in entomology and ecology, interests that later ignited a curiosity about insects as disease vectors. That line of inquiry led him to mapping and geographical information systems. Now he's an HMS professor of biomedical informatics and the chief innovation officer at Boston Children's.

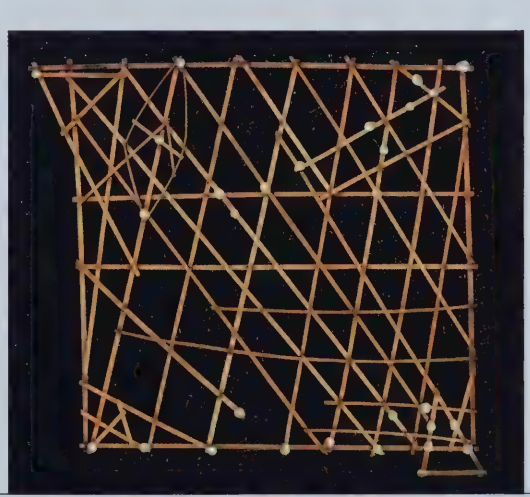
"Geography and health risks are intimately related," he says. "Mapping becomes the foundational concept to understand and communicate those risks."

Some of the connections between health and location seem clear: close proximity to sick people increases one's risk of getting sick, high levels of air pollution go hand in hand with an increased incidence of asthma, and poor health outcomes exist among people living in areas with few or low-quality medical services and limited access to healthy food.

Other connections are more surprising. In a study published this year in *Nature Climate Change*, Brownstein found that an increased resistance to antibiotics was linked to rises in temperature and population density.

In 2006, Brownstein led the team that built HealthMap, the first application to combine data from different sources for use in public health. The tool, says Brownstein, uses open-source software and is designed to be used in a variety of ways.

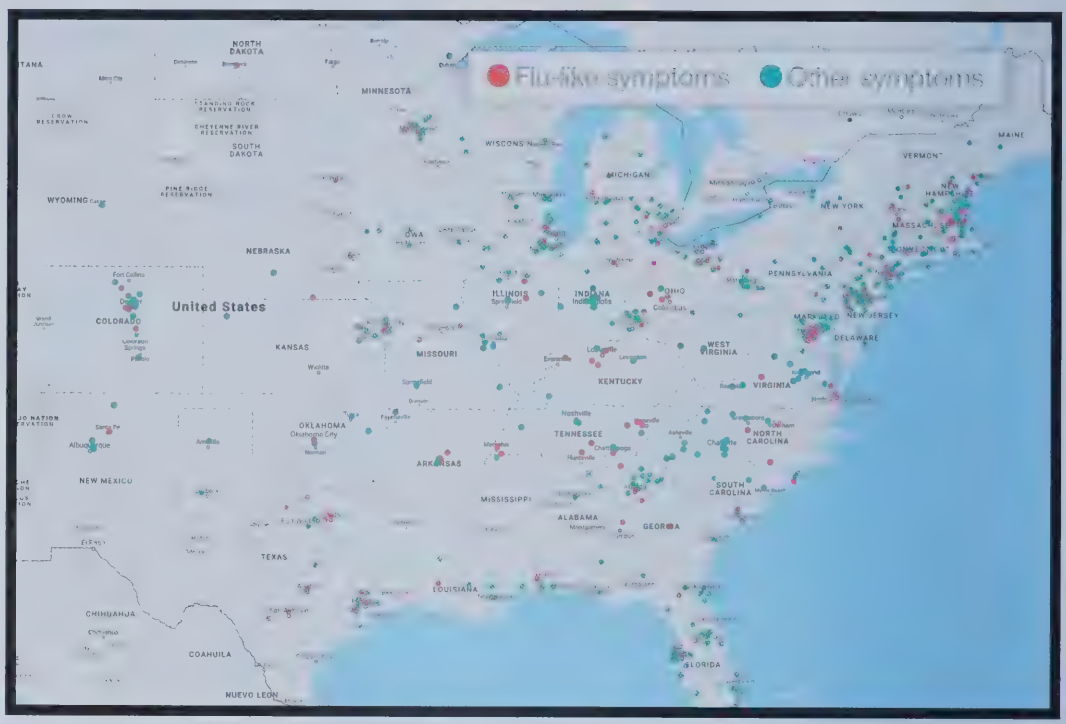
HealthMap tracks the incidence of various conditions in humans and animals—from infections linked to *Acinetobacter baumannii* to pregnancy complications linked to the Zika virus—and monitors other health-related factors like climate and pollution. Software and algorithms generate and update online maps using data drawn from news sources, social media, and other publicly available resources. Brownstein says the tool



Inhabitants of the Marshall Islands used stick maps such as this circa-1920 rebbelib type to navigate the Pacific Ocean by canoe. The map provides sailing directions to atolls and islands (both depicted by seashells that dot the map) in the eastern and western chains of the Marshalls. Straight sticks represent regular currents or waves around low-lying atolls; curved sticks indicate ocean swells.

is being used for everything from outbreak surveillance by global and national health agencies to decision making by physicians in clinics. If a patient who has traveled internationally comes in with a respiratory complaint, her physician can check the map to see if there are outbreaks of respiratory conditions in the region she visited.

While HealthMap depends on data from governmental and nongovernmental sources that can be found online, some of the tools Brownstein has helped develop use geotagged, crowd-sourced data. He notes that the self-reported data that powers the website Flu Near You, for example, details flu's incidence—with high geographic and temporal resolution—at a much lower cost than traditional surveillance methods. In addition, these crowdsourced tools, he says, put "the 'public' back in public health" and provide those who supply the data with heath surveillance news that is customized to show their local risk. This, Brownstein says, adds value for the users and deepens their engagement with the process.



This map on Flu Near You shows mid-August 2018 flu activity in the United States. It was generated by Harvard epidemiologists using reports submitted by members of the general public in the United States and Canada. Flu-like symptoms are shown (red), as are reports of symptoms of other illnesses (green).

Trip advisor

Jeffrey Blossom, who grew up hiking with printed maps in hand, loves to sit with friends around a big paper map, laying out a backpacking trip or identifying little-known pockets of slickrock for mountain biking in the Utah backcountry. He also loves helping researchers build and use digital maps to explore their data.

Knowing where things are happening is an important part of knowing how and why they're happening, Blossom says. Just like people, the factors that affect health, climate, and the rise and fall of civilizations are unevenly distributed across the globe.

"Seeing how these factors relate to one another enables you to understand more about whatever you're studying," he says.

Blossom is the GIS service manager in the Harvard University Center for Geographic Analysis. He teaches cartography and spatial analysis to Harvard students, postdocs, and researchers and helps members of the Harvard community use geographic information systems and maps to better communicate stories with data.

"We're in a geospatial revolution," Blossom says, referring to the quantities of mappable data available from traditional sources, such as federal, state, and municipal governments, and the growing amount of data available from new sources, including crowdsourced and commercially generated databases. While much of the latter may have been collected for marketers, that data—grocery store locations, vitamin supplement purchasing behaviors, and frequency of visits to a doctor, for example—often have applications for social scientists and health researchers.

A map does not need to include multivariate analysis to be useful for health interventions, Blossom notes. In the 2014-2016 Ebola outbreak in West Africa, people in affected communities used OpenStreetMap, a crowdsourced web tool, to map villages not included in commercial mapping products and not visible to imaging satellites because of thick forest canopy.

"It wasn't even disease mapping," says Blossom. "They used the tool to map the roads that would allow first responders to get to where people needed help."

Blossom worked with Lauren Fiechtner, an assistant professor of pediatrics at Massachusetts General Hospital, to produce an interactive map of Boston showing the locations of healthy eating options and places to play and exercise. The maps were used by health coaches working with the families of children dealing with overweight and obesity.

Because most people habitually follow the same routes to and from home, work, and school, and shop in a fixed subset of stores, they often aren't aware of resources that may be available just a block or two off their beaten paths. In a community case study published in *Preventing Chronic Disease*, Fiechtner reported that the health-coaching maps Blossom helped produce increased parental feelings of empowerment. In addition, 76 percent of families who had access to the maps were physically active at new places and 57 percent shopped at new locations during the study's one-year intervention period.

Street sense

Like scattered dots on a map that begin to reveal an obvious pattern at the right scale, the insights gleaned from mapping the spatial dimension of disease can make a big difference in health. For that reason, Brownstein is working to fundamentally change the way the biomedical world thinks about geography. In keeping with physicians who practice social medicine or who study socioeconomic disparities and maintain that you can learn more about the health of a patient by studying their zip code than you can by studying their genetic code, Brownstein wants the idea of geography as a crucial research and clinical tool to become central to mainstream medicine.

"We're just going to keep beating the drum that location needs to be at the core of clinical practice," he says. HM

Jake Miller is a science writer in the HMS Office of Communications and External Relations.

in 5

A conversation with Sun Hur, HMS associate professor, Department of Biological Chemistry and Molecular Pharmacology

JUSTIN SQUARES

You research the mysteries of immunity—how the body recognizes self from other. What sparked this interest?

I was always interested in physics. I like its simplicity, its beauty and elegance, the fact that it allows you to describe a complicated phenomenon using only first principles. Over time, I also learned the beauty of "messiness" and became fascinated by the process of pulling individual threads from a tangled mess. Self/nonself RNA discrimination in immunity seemed like an interesting mess that I could work on. It also has a philosophical implication about self-identity, which I like.

What is your ultimate research quest?

There are two pathways I'm interested in. One deals with the innate immune discrimination between self and nonself RNA. The other is sort of an RNA quality-control system that spots correctly folded, and misfolded, cellular RNA. Researchers don't understand misfolded RNA well. It is one of my hypotheses that when RNA is misfolded or has not degraded properly, it can be misidentified by the immune system as nonself. I'm interested in that interface between RNA quality control and immunity and the role it may play in a range of diseases.

You grew up in South Korea. Does experiencing different cultures and new places hold any instructive lessons for scientists and scientific inquiry?

I think it's important to be outside of one's comfort zone, to be comfortable with being uncomfortable. I am a woman; I am Asian. I feel like an outsider everywhere I go, so I'm used to exploring new things from the outside. Maybe that indirectly affects how I choose a project or how I ask a new research question. When you are an outsider in a given field, you are more likely to detect dogmas or gaps in a line of research.

What are you most proud of?

I am most proud of the pain I've overcome. When I was in high school, the pressure to do well academically was enormous. In fact, some of my classmates and two of my cousins committed suicide. I developed a phobia that impaired my ability to function. I overcame it when I realized that whenever I worked on something I enjoyed, such as solving math problems, I completely forgot my fear.

When I started my lab, our first paper kept getting rejected. I felt the world was against me. I told myself, 'This may be the last paper you write, so just focus on writing a good paper and don't worry about anything beyond that.' I learned that when you are in a tough situation you can either give it everything or devote part of your energy to finding an exit route. The thing is, if you are looking for a plan B, you're aiming for the failure of plan A.

If you could do anything else, what would it be?

When I was young I was torn between becoming an artist and becoming a scientist. Right now, I'm channeling my passion for painting and injecting my artistic vision into my son. I get a lot of joy from that.

—Ekaterina Pesheva

A collection of images, taken of cadavers, helped lay the foundation for the clinical use of x-rays

Ernest Amory Codman received his medical degree in 1895, the same year that Wilhelm Roentgen made the iconic image of his wife's hand, the first roentgenogram ever taken.

Codman, having caught wind of this discovery, was eager to explore it himself, and in 1898 published a series of x-ray images for the study of anatomy. In that paper, Codman wrote about how the "x-ray can do what the knife and frozen section cannot."

Human bones, Codman noted, could now be seen in the context of their natural placement within the body, with outlines and differing densities visible. Arteries could be visualized by injecting them with a mixture of starch and a red mercuric salt, allowing smaller blood vessels to be "seen in a way impossible in dissection."

Codman partnered with John Trowbridge, a professor of physics at Harvard, and Elihu Thomson of General Electric in Lynn, Massachusetts, to develop "x-radiation" for clinical use. He became one of the nation's first skiagraphers, or "shadow writers," as radiographers were then known.

Codman's skiagraphs, taken of cadavers, presented images of joints in positions unlikely in a living person. Using an early fluoroscope, he was one of the first to delve into the biomechanics of joint movement, measuring extremes of flexion and extension. He thought his pictures of normal joints would be useful in forming image series to compare with pathologies. Of all the joints, Codman considered the wrist to be the most interesting and found its movements "very beautiful."

In 1902, Codman published a paper using case studies of accidental x-ray burns to discuss, categorize, and analyze the many factors that can contribute to these burns, including "intensity of current used to stimulate the tube, the quality of the tube, the distance and time of exposure, and the idiosyncrasy of the patient."

Patients were not the only ones at risk of radiation burns: A condition known as skiagrapher's dermatitis began to appear in scientific papers not long after Roentgen's discovery. Skiagraphers, likely including Codman, did not use protection in the early years, and many experimented on themselves to ill effect. The risks were known—Elihu Thomson in 1896 published a warning and a recommendation that the head of the x-ray apparatus be enclosed in a box with a hole only large enough for the x-ray beam to break through.

—Susan Karcz

In his album of x-rays of a cadaver, Ernest Codman presented images of a range of anatomical structures. Each image illustrates the detail that could be captured in "skiagraphs."

Student Life

Since its founding two decades ago, the Paul & Daisy Soros Fellowships for New Americans has supported more than fifty HMS MD students as fellows. To help celebrate this milestone, we introduce the HMS 2018 Soros Fellows: Jamaji Nwanaji-Enwerem, Suchita Nety, and Asmaa Rimawi.

Asmaa Rimawi

The summer has been a busy one for Asmaa Rimawi, a rising third-year medical student at HMS. Classes, followed by clinics, followed by the beginning of her surgical rotation have filled her days.

Yet, Rimawi, MD 2020, still finds time to research the effects of discrimination on health and on the delivery of health care. Whether it's her service on the dean's task force on diversity and inclusion, her participation in the School's efforts to recruit students from populations traditionally underrepresented in medicine, or her efforts to establish a clinic in the mosque serving the Islamic community where she grew up in Brooklyn, New York, Rimawi seeks to further improve how medicine serves all people.

"Serving as my mother's translator in clinical situations at a young age made clear it to me that our medical system is not equipped to handle patients from a variety of backgrounds, cultures, and languages," recalls Rimawi. "As I grew older, I learned about the source of some of these gaps in care. I learned about how a patient's wait time before securing a doctor's appointment can depend on form of payment, how much the infant mortality rate changes depending on the color of a baby's skin, and how access to basic necessities of health, from affordable healthy foods to crucial medi-

cations, is limited in most populations. To me, health care became the ultimate testament to equity, a reflection of the progress our society had yet to make."

"I was motivated to go into medicine to explore these gaps in care, to understand the role doctors can play in advancing the conversation on discrimination in this country," she adds, "and to learn how much my mother's experience in the health care system was affected by the scarf on her head or the language she spoke."

Rimawi's time in clinic has reinforced the value that patient interaction holds for her.

"I think the ability to meet so many different people and almost instantly form a relationship with them is something unique to the profession of medicine," says Rimawi. "As a physician, I have to build a therapeutic alliance with my patients, sometimes within minutes, if I hope to be a part of the decisions they make regarding their health. This, for me, is both a privilege and responsibility."

Suchita Nety

Suchita Nety, MD-PhD 2025, is in the second year of her medical school training. As a student in the Harvard/MIT MD-PhD program, she's been spending the past few months determining the lab in which she will pursue her thesis work.

"I'm using CRISPR to study genes that are involved in cancer immunotherapy," she says of work she's doing at the Broad Institute of MIT and Harvard. "As an undergraduate I became interested in synthetic biology, which is genetically engineering cells so that they can perform different tasks. It's work that takes inspiration from electronics, programming circuits to perform logical operations. We're trying to translate that paradigm into cells so they can analyze information from their environment and perform actions based on that information."

Nety is, in short, hoping to make cells behave as computers. And she hopes to use such programmable cells to target tumors.

During her undergraduate years at Caltech, Nety studied chemistry and thought a career in research was in her future. Then she shadowed clinicians at a hospital nearby.

"It was the most transformative experience I've had," she says. "I felt privileged to watch the very intimate interactions that occurred between physicians and patients. I had no idea medicine could be like that."

From that experience, Nety developed an interest in medical oncology—and a focus for the research she would pursue. She also realized how powerful patient visits can be.

"I want to be a physician-scientist," Nety says, "and run a lab that develops synthetic biology technologies that can be applied to different diseases." She does, however, want to keep in touch with patients who could benefit from those technologies. From early experiences in her program, she knows how profound it can be to talk with patients who may benefit from the work being done in a lab.

"Sometimes the divide between lab and patient can be vast," Nety says. "I think every physician-scientist's goal should be to bridge that divide."

Jamaji Nwanaji-Enwerem

Since he was in middle school, Jamaji Nwanaji-Enwerem, PhD '18, MD 2020, has known he wanted to be a physician. The urge to couple that with research, however, was planted in the spring of his senior year in high school, the result of a call from a professor at Morehouse College.

"I was going to attend Morehouse," Nwanaji-Enwerem recalls, "and she told me that Morehouse had a one-month-long summer research program I could participate in if I was interested. Although I couldn't put my finger on exactly what she meant by research, I was interested."

That summer experience proved pivotal. Throughout his undergraduate years, Nwanaji-Enwerem immersed himself in scientific inquiry. As part of the Dr. John H. Hopps, Jr. Research Scholars Program, he worked with science professors during the fall and spring semesters at Morehouse. Then, each summer he went to a different school where he participated in other "truly enriching research experiences."

Of all the sciences, he developed an early interest in genetics. At Harvard, that interest has gained definition in the Program in Biological Sciences and Public Health.

"I had a molecular wet science background," he says. "The program gave that molecular science a home within the realm of public health." In his research at HMS, Nwanaji-Enwerem has investigated how different environmental exposures affect health. His particular focus has been on understanding how exposure to airborne particulates affects biological aging via epigenetic processes.

"I like the way research has taught me to think," he says. "Solutions to problems do not come from something I've memorized but from my struggling with questions and trying to figure out something new, something no one else may have considered before."

This questioning approach is one Nwanaji-Enwerem believes will enhance his work as a physician. "You're always trying to figure out, based on a constellation of symptoms, what disease a patient has," he says. "I think about the possible diagnoses and about the diagnoses that are possible but less likely."

"As an MD-PhD," he says, "I know I'll have a career that will give me the chance to care for individual patients while also allowing me to contribute discoveries that can further benefit medicine and population health."

Finding **Aid**

MAPS ARE CRUCIAL to successfully fighting forest fires. Just ask radiologist John Crues.

"We used topographic maps to plan the best attack route—it's harder to fight a fire on steep terrain because it spreads more rapidly up a mountain slope. So you design where best to put your fire lines."

Crues continues to rely on maps, although his mapping tool has changed. Now this medical director and vice-president of RadNet, a national chain of imaging centers based in Southern California, uses radiologic images and radiology tools to navigate and map the human body, much as he and his fellow smoke jumpers used topographic maps to plan their fights against forest fires.

Crues had just entered the field of radiology when magnetic resonance began being used medically. That proved to be great timing for the young physician.

Before settling on medicine as his profession, Crues had intended to study physics. Medicine, he decided, provided the human connection missing in the physics lab. At HMS, he learned of the HST program and was able to do his first two years' course work in tandem with students in the program.

Near the end of his residency at Cedars-Sinai Medical Center in Los Angeles, the hospital began installing a high-field magnetic resonance scanner, one of the first such instruments in the world. Crues helped with the installation and, after residency, became Cedars-Sinai's first director of magnetic resonance imaging.

Together with colleagues, Crues conducted some of the early research on the use of magnetic resonance to image the musculoskeletal system, particularly knees. With a colleague, he also conducted pioneering investigations of how humans handle heat load and temperature changes during a magnetic resonance scan.

"An MR scanner is a big microwave oven," he says, "and one of the concerns was what physiologic effects that heating would have on the human body." They showed the technology was safe for humans, findings that were pivotal to the developing field.

Crues now combines clinical work with running a training program in magnetic resonance for specialists located at his company's various sites and for individuals who, as invited fellows to the program, come to the company for training. Crues lectures daily to program participants and posts the lectures online for use by radiologists worldwide.

According to Crues, magnetic resonance has changed sports medicine and orthopedics. The next big change: the use of artificial intelligence. The quantitative information it provides, Crues says, will allow greater precision in reading images. —*Susan Karcz*

John Vernon Crues III, MD '79 | Medical Director and Vice-President, RadNet

JOHN DAVIS

The Sound of Glass **Shattering**

A century ago, Alice Hamilton became the first woman to be appointed to Harvard's faculty

BY ELEANOR AND MILES SHORE

It could be argued that it took a world war to get a woman appointed to the faculty of Harvard University.

As World War I was ending, HMS had begun to assess the war's effects on the goals of the School. A certain number of graduates, it found, had the talent and training to provide public service in many ways beyond solely providing clinical care. To translate this knowledge into action, the School's leaders decided they should add to its primary focus on educating clinical practitioners.

In his 1918-19 report to A. Lawrence Lowell, the president of Harvard, HMS Dean David Edsall noted, "federal and local government and bodies related thereto, commercial and social organizations and others have many problems of health that are of humane or economic importance." Edsall had further evidence for the depth of support for such an initiative; he had accumulated $325,000 from industrial corporations to fund research and teaching concerning these health problems. As a result, Edsall sought to expand the HMS curriculum to include preparing students for careers in public health and industrial health.

To realize this new direction, Edsall proposed appointing Alice Hamilton, whose work in industrial health had pioneered the field in the United States. Hamilton had come to his attention during their work as members of a National Research Council committee on munitions workers.

He had another reason for suggesting Hamilton, however. Edsall was aware that Harvard was beginning to stand out for its failure to enroll women as students or appoint them as faculty. He addressed the issue in a letter to President Lowell, "I should be very glad to know that there would be no objections to appointing her because of her sex. ... I would emphasize the fact that she is greatly superior to any man that we can learn of for such a position."

In December 1918, Edsall offered Hamilton an appointment as assistant professor of industrial medicine to participate in teaching medical students a new curriculum in that field and continue her research in industrial health. By March of the following year, her appointment was confirmed in a meeting of the President and Fellows of Harvard College.

A portrait of Alice Hamilton by German photographer Emil Otto Hoppé, circa 1915 to 1955.

Reflecting on her appointment in her autobiography, Hamilton wrote, "I was told that the Corporation was far from enthusiastic ... and that one member had sworn roundly over it. But then said my informant, 'you know he always swears.'"

Groundswell

Hamilton's path to the appointment at Harvard had been long and winding, yet she had persisted because she recognized that it would validate her work and the role of women in science and academia.

She was right. Her appointment generated a flood of news stories across the country. Clippings archived at Harvard's Pusey Library come from newspapers in California, Illinois, Massachusetts, Montana, New York, Ohio, and Wisconsin.

Asked by a woman reporter from the *Boston Herald* whether women should be admitted to the Harvard Medical College, she

Her personal development was marked by competing urges—intellectual satisfaction versus service to others. Should she be an academic researcher or a missionary?

SCHLESINGER LIBRARY, RADCLIFFE INSTITUTE, HARVARD UNIVERSITY (LEFT AND ABOVE)

responded, "Of course I believe in admitting women to Harvard. Isn't it the last stronghold that is now against them? All the other first-class medical colleges admit women. And if women want to make medicine their profession, surely, they should have the best schools open to them for their study. I'm afraid I'm too western, with too many coeducational experiences, to grasp a situation where the line is drawn between men and women students … I am not used to considering questions of women's education apart from those of men's."

When Hamilton accepted the appointment at Harvard, she did so with the proviso that the appointment should be half-time, leaving her free to continue her field work studying the dangerous trades. Harvard, too, set stipulations: She must not enter the Faculty Club, march in the commencement procession, or receive football tickets, a perk highly prized by the male faculty. Her ticket to the commencement platform sternly warned "under no circumstances may a woman sit on the platform."

Thirst for learning

Born in 1869, Hamilton was brought up in Fort Wayne, Indiana, in a family of four girls and one boy that, with a platoon of cousins, was

its own little society. Sustained with some difficulty by money inherited from a pioneering grandfather, the family offered the children schooling at home. The curriculum emphasized languages, literature, and history, supplemented in late adolescence by two years at Miss Porter's School in Connecticut. Arithmetic and science were not offered either at home or at Miss Porter's.

Her personal development was marked by competing urges—intellectual satisfaction versus service to others. Should she be an academic researcher or a missionary? The choice of medicine offered a way to do both. Her medical training was haphazard at first. After private tutoring in mathematics and science she spent two years in what she regarded as a third-rate medical school in Indiana before being admitted as a special student in the medical department of the University of Michigan. Michigan offered a medical curriculum that emphasized science, early exposure to clinical work, and an intellectual atmosphere that Hamilton relished. It also was receptive to women students; nearly 30 percent of the students in her class were women.

She graduated from Michigan in 1893 and accepted internships at Northwestern Hospital for Women and Children in Minneapolis and later at New England Hospital for Women and Children in Boston. Although determined to be a career scientist, she wanted clinical experience to broaden her approach. Unfortunately, inadequate supervision and general disorganization at both institutions led her to leave before completing her program. By 1895 she was again at Michigan, this time for a one-year appointment as a resident graduate and lab assistant to Frederick G. Novy, a distinguished bacteriologist.

Following a year in Germany with her sister Edith, who later became a noted author on classical Greece and Rome, Hamilton went to Johns Hopkins University Medical School, where she worked on anatomical pathology with Simon Flexner, then a young pathologist. She also became acquainted with that school's five founders, including surgeon William Halsted, gynecologist Howard Kelly, clinician William Osler, and bacteriologist William Welch, each a giant in medical research and education. She delighted in the intellectual stimulation and discipline, as well as the brilliance of the men she worked with, who accepted her "without amusement or contempt or even wonder."

When the year was over, she accepted a position to teach pathology at the Women's Medical School of Northwestern University in Chicago. A dividend of that position was the opportunity to live at Hull House, already the most famous settlement house in the United States.

Originally, Hull House had been a mansion on Chicago's West Side, but by 1893 it was a relic in a chaotic slum peopled by desperately poor individuals, both immigrant and native-born, living in dilapidated houses with open latrines. Alcoholism, crime, and poor health further crippled their lives. The settlement house movement sought to alleviate such conditions.

While she was in Indiana, Hamilton had attended a lecture by Jane Addams, the founder of Hull House. The presentation sparked Hamilton's imagination, and she became excited by the adventure of knowing Addams and participating in settlement life. Here lay Hamilton's opportunity to realize her long-held wish to be of service.

Hamilton, circa 1940s, stands in her garden in Hadlyme, Connecticut (far left).

At its semicentennial celebration in 1936, Newcomb College, the coordinate women's college of Tulane University, conferred an honorary doctor of science degree on Hamilton (center, above).

In 1995, the U.S. Postal Service issued a stamp commemorating Hamilton's contributions to the field of industrial medicine and to social reform.

The relationship became a mainstay for Hamilton. For nearly forty years, Hull House was a home base to which she returned regularly from participation in world affairs.

Industrial strength

Hamilton's career in industrial health came together slowly as her Hull House experiences multiplied. Faced with the realities of dangerous working conditions among her Chicago neighbors, she was surprised to find that the United States had no provision for the prevention and treatment of, and compensation for, industrial injuries. She attributed this lack of interest to the field's status as one "tainted with socialism or with feminine sentimentality for the poor."

Hamilton educated herself in the literature from countries where industrial health was an established branch of medicine, and studied a Chicago typhoid epidemic. That preparation proved useful; she was one of the initial appointees to the Illinois Occupational Disease Commission, the first of its kind in the nation. During her tenure on the commission and afterward, she was the pivotal researcher for a study published in 1911 that investigated the occupational hazards of lead, arsenic, brass, carbon monoxide, the cyanides, and turpentine. As the study's managing director, she assigned herself lead poisoning. Employing what she termed "shoe leather epidemiology," she became an expert on the intricate industrial processes that involved lead.

Her industrial-health career accelerated when she took leave from the Illinois work to attend an international conference on occupational accidents and diseases in Brussels. Her participation there resulted in an invitation from another attendee, Charles O'Neill, then commissioner of labor in the U.S. Department of Commerce, to conduct a national study of lead in industry. She left academic research and devoted herself enthusiastically to a new life "that was scientific only in part, but human and practical in greater measure."

Her success was entirely the result of her personal charm and relentless focus. Working in the era of the great muckrakers—who used confrontation to promote change by shaming and guilt—she took a different tack.

Hamilton's approach assumed that the factory owners, managers, and foremen wanted to improve the health and safety of workers but needed factual evidence of problems. She supplemented direct factory visits with combing hospital records to calculate the toll of sickness and injury.

This approach was grounded in lessons from Hull House. There, Hamilton had learned the power of first establishing a friendly relationship with those in charge and then drawing upon those peaceful relations as one steadily pushed toward one's goal.

This astute technique proved successful in her investigations of a range of dangerous working conditions: phosphorus poisoning in match manufacturing, silicon dust as a respiratory hazard in enameling, carbon monoxide exposure in the steel production industry, and the physical toll of working twelve-hour days seven days a week.

She was surprised to find that the United States had no provision for the prevention and treatment of, and compensation for, industrial injuries.

It was her careful documentation of this work and publication of her findings that prompted Edsall to support her for the HMS appointment.

The 1920 HMS catalog listed Hamilton's industrial toxicology lectures as occurring twice a week during the fall term. Two years later, in a report to President Lowell, Edsall proposed the need for a separate school of public health. He felt such a development would "prove to be the most important one for many years in its influence upon the future prominence and activity of the Medical School."

With the establishment of the separate school, Hamilton began teaching the toxicology course as a member of the public health school's faculty. While there, she published two books, *Industrial Poisons in the United States*, in 1925, and *Industrial Toxicology*, in 1934.

Inconvenient truths

Hamilton's commitment to humanitarian service also continued. Following World War I, she participated in the Quaker efforts to relieve starvation in Germany and served on the health committee of the League of Nations. She was a vocal advocate for birth control.

She traveled in both Germany and Russia as their governments evolved. In Germany, she was appalled by the Nazi persecution of Jews and the growing threat of fascism. Soon her commitment to pacifism melted into strong support for World War II. In the 1950s, her political interests and associations multiplied as the tide of McCarthyism threatened civil liberties and freedom of speech in the United States. She joined a host of prominent intellectuals and other public figures caught up in the anticommunist furor of that time, associations that some speculate resulted in an FBI file.

In her retirement years, she began consulting for the U.S. Department of Labor, Division of Labor Standards, and, with Harriet Hardy, an occupational medicine specialist and the first woman full professor in a clinical department at HMS, revised her seminal text, *Industrial Toxicology*. She also received multiple awards, including the prestigious Lasker Award, presented for her contributions to workers' health. She was the first woman to receive a Lasker.

In full retirement, she moved with one of her sisters to a colonial farmhouse in rural Connecticut to garden and keep up a vigorous correspondence with her old friends and contemporary political figures, such as jurist Felix Frankfurter. She died on September 22, 1970, at the age of 101.

Throughout her career, Hamilton fought with graceful determination what she described as the feudal organization of industry, in which the owners of companies, as "lords," wielded immense power over the "serfs," the immigrants and unskilled laborers who worked for them. Her work to protect the health and safety of ordinary workers remains as important today as it was a century ago when this visionary researcher and citizen of the world became the first woman to be appointed to the faculty of Harvard University. HM

Eleanor G. Shore, MD '55, MPH '70, retired as the HMS Dean for Faculty Affairs in 2004; Miles F. Shore, MD '54, is the HMS Bullard Professor of Psychiatry, Emeritus.

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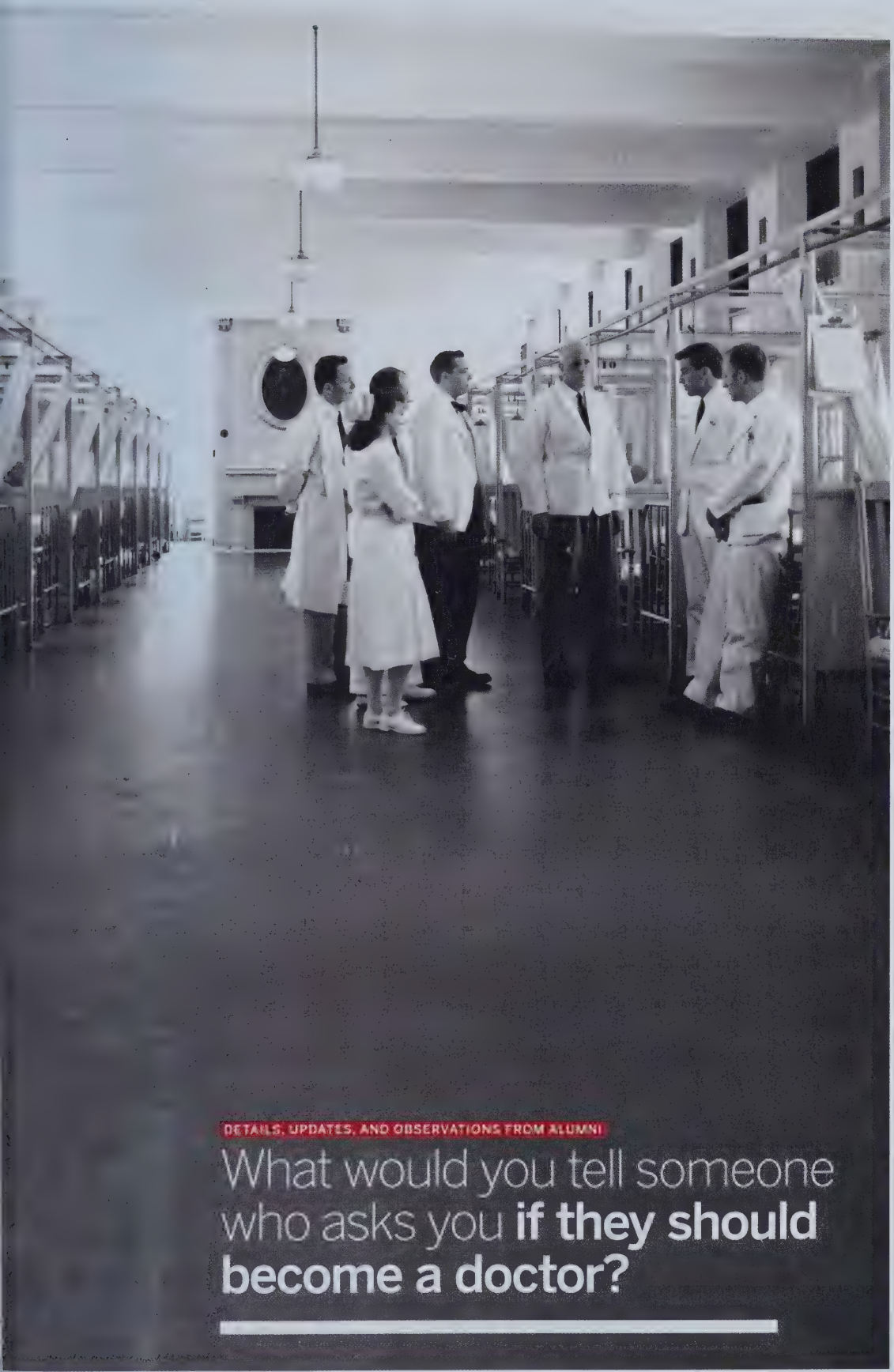


In this mid-twentieth century photo, William Bosworth Castle, MD 1921 (center) talks with medical staff and faculty in a ward at Boston City Hospital.

DETAILS, UPDATES, AND OBSERVATIONS FROM ALUMNI

What would you tell someone who asks you **if they should become a doctor?**

Redmond Burke, MD '84

You should become a doctor if you want to push yourself to the human limit during a decade or more of training and learn from a generation of brilliant people. You should become a doctor if you want to wake up every day without an alarm and know that you are going to save someone's life, or their baby's life, or make them feel better, or invent a lifesaving drug, or simply know that whatever you do that day, you will help someone. That's what it is to be a doctor, and it's a phenomenal feeling.

Victor Connell, MD '74

I would say that it depends on which kind of medicine he or she would like to practice. Managing a primary care practice has become very challenging, given the current trends toward physicians becoming employees of large managed-care organizations and greater government involvement in health care delivery and reimbursement. The expense involved in becoming a physician is also a big factor, so it is worth considering alternative health care provider options such as nurse practitioner, physician assistant, and physical therapist.

"Being a medical doctor has allowed me to keep alive the hope I had when I was a student at HMS: to make the world a better place."

Thomas Ukena, PhD '74, MD '75

As I told my daughter, who is now an endocrinologist, medicine is not a perfect career, but it's way ahead of whatever is in second place.

John Bullock, MD '68

I would tell them to do it only if they were 100 percent devoted to medicine.

Kurt Isselbacher, MD '50

In the current climate, I would hesitate.

James Alonzo Nelson, MD '65

If it is a true calling, there is no better career. Keep learning as long as you can and seek ways to improve patient outcomes. The breadth of medicine allows creative and rewarding opportunities encompassing a range of fields and employment choices. I chose an academic pathway, which I enjoyed immensely despite some political obstructions.

Elliott Miller, MD '58

Have a passion for medicine or don't go into it. If you don't have that passion, it will be too hard.

Hatim A. Kanaaneh, MD '68

I would strongly recommend a life as a physician. Being a doctor has allowed me to not only care for people who might feel uncomfortable or even afraid to visit a doctor, but has also allowed me to build bridges between people. As a physician, I feel I have been able to change a corner of the world for the better.

When I graduated from Harvard with an MD and an MPH, I made the decision to return to Arrabeh, my Palestinian home village in Galilee, North Israel. I was the first indigenous medical doctor serving a region of more than 50,000 people. Today, Arrabeh boasts the highest number of medical graduates per thousand in all of Israel, possibly the world. Perhaps more important, in our region of Israel, health worker development is the one arena that suffers the least differential between the Jewish majority and the Arab minority. This is, to me, a miracle, one that Harvard inspired.

Using my skills in medicine and public health, I have set up institutions to help my people. One, the Galilee Society, an association for health research and services that I founded with three colleagues, is a nongovernmental organization that addresses unmet health and development challenges in Palestinian minority towns and villages in Israel. In 1998, with a young neuropsychologist from my village, I co-founded Elrazi, the first Arabic-language child rehabilitation center in Israel. This center continues to thrive, with scores of specialists and half a dozen branches across the country.

I am now retired and have begun writing in English so that I may tell the world about delivering care in a region so often troubled by conflict. As a physician and a voice within Israel, I want to let the world know that peace is possible between Arabs and Jews in historical Palestine.

I have Harvard, and my dear wife, to thank for the support and inspiration I received while a student at HMS. Today, if someone asked me about becoming a doctor, I would tell them that, for me, being a medical doctor has allowed me to keep alive the hope I had when I was a student at HMS: to make the world a better place.

Richard Krueger, MD '73

Yes, it is a wonderful profession, but one that is undergoing great change.

Mary Flowers, MD '78

Enter the profession with passion, grace, and gratitude for the opportunity to serve humankind. Don't become a doctor to be a "provider." I think that insurance companies knew that calling doctors providers would undermine the public's confidence and trust in and respect for doctors as professionals. Being a doctor requires sacrifice, commitment, and resolve. Being a provider allows us to push pills, earn a salary, and go home. There is a definite distinction!

Ernie-Paul Barrette, MD '90

Medicine remains a noble profession. Do not let anyone convince you otherwise.

Nason Hamlin, MD '72

If they want a profession that is never boring, that requires hard work, that brings them in contact with wonderful people, and that helps to relieve human suffering, there is no better profession in the world.

Tamara Fountain, MD '88

If you want to feel the pressure of encapsulating a 135-page electronic medical record, taking a history, performing a physical and counseling a frightened, vulnerable patient—all in 15 minutes—become a doctor.

If you want the solemn privilege of asking the most intimate of questions and examining the most private of body parts, become a doctor.

If you want to make a palpable difference in or literally save someone's life, become a doctor.

William Thorpe, MD '73

Do it for the right reasons—mixing science and humanity in a most intimate way.

Joan Leary Martinez, MD '66

Follow your heart!

Mark Perlroth, MD '60

It is certainly one of the most rewarding professions intellectually and personally. It provides satisfaction in many ways, including the appreciation and respect of your patients, co-workers, and society.

It entails rigorous training and sleep deprivation and, depending on your choice

of specialty, can remove you from the pleasures of home and children.

At the end of your career, however, you can look back without the sense that your efforts and choices were spent wastefully or frivolously.

Sarah Wood, MD '95

I'd tell them that if they have a true passion to be a physician, and if they are going into it for the right reasons, then there is no better profession. It is an incredible honor to be part of your patients' lives during their most vulnerable and challenging moments, but one must be willing to endure long years of training, hard work, and the complexities and frustrations of a health care system that can often erode a doctor's compassion and motivation.

Ryan Chuang, MD '03

It's a great profession, but it comes with lots of sacrifices as well.

Herbert Adams, MD '65

The journey is tough, but the life is so worth it. Being a doctor will change how you see the world and how it sees you for your whole life.

Richard Reiling, MD '67

Medicine is a mobile platform, but despite all the changes it is and always will be a great and honorable profession. The pain and joy of medicine are found in the care of the sick, the healthy, the poor, the rich, the young, and the old. Enter the profession with a goal of relieving the pain and suffering of others and ignoring your own frustrations and pain.

Albert Menno, MD '56

I would tell them that medical school and medical practice are much different now than from when I trained, but it is still worth going into medicine if they have a sincere compassion for and interest in helping people.

Ronald Tegtmeier, MD '68

Being a physician is still a great and noble profession. Compared to previous generations, you would have less independence, less monetary reward, more paperwork, and more people second-guessing you. But if you keep your heart and mind on the goals of helping people with compassion and science and of advancing medicine, you can have a rewarding and gratifying career.

Kelly Orringer, MD '94

Yes! It remains a privilege and a joy to get to know my patients, their parents, and the wonderful colleagues, students, and trainees that I meet on a daily basis as a general pediatrician.

David Altshuler, MD '90, PhD '90

Medicine is always changing, but certain things are constant: There will always be people in need of care, there will always be a valued place for caregivers who are knowledgeable and kind, and there will always be mysteries of the human body to solve. From a more practical standpoint, society will always need doctors. If you are motivated by an interest in humanity and a desire to serve, medicine is a great career.

Richard Peinert, MD '73

There are two groups of people who are never "ex:" Marines and doctors. To the youngsters reading this, you will understand this truth better as you approach retirement. You may hate the paperwork, the insurers, and the bureaucrats, but nothing surpasses the joy you will share with your patients. They will start as your patients, progress to patients with whom you are friendly, and finally become friends you have the great privilege of caring for. It is a sacred and beautiful trust.

Ellis Rolett, MD '55

Both the opportunities and challenges are greater than they were when I was in medical school. A career in medicine today can be more impersonal than it was in my day. Be on guard against that if you want medicine to be a satisfying career.

Kathryn Glatter, MD '93

Being a doctor is fun and a great way to help others. I'm an electrophysiologist, or interventional cardiologist, and it's an extremely interesting, satisfying career. I would do it again in a heartbeat.

Howard Rubenstein, MD '57

My answer would depend on the someone who's asking the question. I was a premed adviser at Kirkland House. I wasn't impressed with the motivation of many premeds, even though they got straight As and were readily accepted. One fellow stood out. He cared deeply, related well, had a sense of humor, was sincere, and had integrity, but his grades were mostly Bs. He was rejected by all his choices. When I called the schools, a typical response was, "We want a scientist, not a person of integrity." I sure hope things have changed.

Peter Zawadsky, MD '68

Make certain you have an awareness of what kind of personal as well as professional life you would like to have in both the short and long term. One of the biggest hazards of a medical career is becoming overly committed, which can lead to burnout. Remember: "Life is short, art long, opportunity fleeting, experience treacherous, judgment difficult."

Joseph Parrish, PhD '69

Do you like to learn and to teach medicine? Physicians need a good sense of who they are and an uncanny ability to quickly find hints of what a person's malady is and follow up with the tests and procedures needed to develop a treatment plan. They must function as a member of a team of physicians, nurses, lab technicians, and other specialists in order to effectively treat all sorts of diseases and complaints. Mental health is always at risk for an overworked doctor, so watch for the need for self-healing.

Edward Ussery, MMS '08

People who think like computers will be replaced by them. Never lose your humanity.

Sean O'Connor, MD '82

Go for it. It will be different, but it's still a great career.

Thank you to everyone who offered guidance and a glimpse of the role medicine has had in their life.

The next issue of Harvard Medicine *will feature your responses to the question:* ***What issues would you like to see researchers address to further advance women's health?***

Responses can be submitted online: https://hms.harvard.edu/rounds; via email: hmsalum@hms.harvard.edu; by phone: 617-384-8520; or by mail: Rounds, Alumni Affairs and Development, Harvard Medical School, 401 Park Drive, Boston, MA 02115.

Obituaries

1940s

1943

Irving M. London, MD
May 23, 2018

Isadore N. Rosenberg, MD
February 2, 2018

1946

William C. Van Buskirk, MD
May 27, 2018

1947

David D. Beiler, MD
June 8, 2018

James H. Thomas, MD
March 9, 2018

1948

Thomas O. Lohr, MD
March 13, 2018

1950s

1950

Richard H. Allen, MD
April 22, 2018

Robert H. Clifton, MD
February 23, 2018

Frank W. Lane, Jr., MD
November 28, 2017

John H. Parks, MD
December 13, 2017

1951

Ray K. Brown, PhD
June 1, 2018

Murray Strober, MD
March 17, 2018

1952

William R. Buchanan, Jr., MD
March 21, 2018

Wesley G. Byerly, MD
December 12, 2017

Bradford W. Lundborg, MD
September 19, 2017

James W. Murphy, MD
May 6, 2018

1953

Frank V. Colombo, MD
May 1, 2018

1954

David W. Allen, MD
March 2, 2018

1955

Barbara E. Wright, MD
December 3, 2017

1956

John H. Milne, MD
March 14, 2018

1958

Howard E. Adkins, MD
May 23, 2018

Jed L. Howard, MD
November 27, 2017

Bernard T. Hutchinson, MD
April 9, 2018

Lyman E. Sproul, MD
April 15, 2018

1959

Boyd R. Burkhardt, MD
May 7, 2018

James J. Sidd, MD
May 18, 2018

Elliot S. Vesell, MD
July 23, 2018

1960s

1960

Roland E. Houle, MD
May 16, 2018

1961

Larry G. Seidl, Jr., MD
April 13, 2018

1963

Robert R. Foster, MD
April 19, 2018

Edward E. Hazen, Jr., PhD
December 5, 2017

Bradley T. Troost, MD
November 13, 2017

1964

Jonathan M. Himmelhoch, MD
November 24, 2017

1965

Kenneth H. Falchuk, MD
May 3, 2018

Robert H. Rubin, MD
June 3, 2018

1967

Katherine A. Forrest, MD
May 16, 2018

1970s

1972

Diane Kittredge, MD
June 4, 2018

1973

Hardin C. Jones, MD
December 28, 2017

1974

Walter Jaros, MD
February 5, 2018

1975

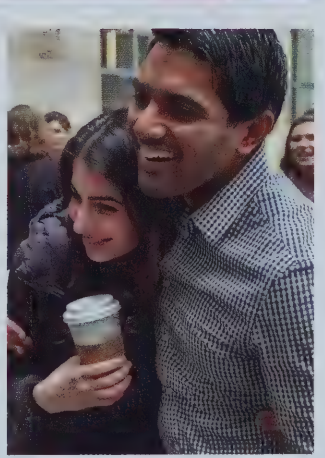
Charles I. Krauthammer, MD
June 21, 2018

1980s

1988

Jeffrey L. Hanway, MD
March 9, 2018

This listing of deceased alumni includes those alumni whose notices of death were received between April 1 and July 31, 2018.



Match List **2018**

ANESTHESIOLOGY

Betty Erfe
Northwestern McGaw

Carlos Estrada Alamo
Hospital of the University of Pennsylvania

Christine Kuo
University of California San Francisco

Johanna Lee
Massachusetts General Hospital

Mary Morales
Brigham and Women's Hospital

Sarvagna Patel
Stanford University Programs

Yu Shao
Duke University Medical Center

DERMATOLOGY

Severine Cao
University of Michigan Hospital

Ricardo Guerra
University of Virginia

Ryan Karmouta
UCLA Medical Center

Lauren Ko
Massachusetts General Hospital

Jennifer Lo
Massachusetts General Hospital

Andy Nguyen
New York University School of Medicine

Michael Nguyen
University of California Irvine Medical Center

Connie Shi
Massachusetts General Hospital

Hannah Song
Massachusetts General Hospital

Sally Tan
University of California San Francisco

Fan Di Xia
Massachusetts General Hospital

EMERGENCY MEDICINE

John Arevalo
University of Chicago Medical Center

Kaitlen Howell
Alameda Health Systems

FAMILY MEDICINE

Jillian Moore
University of New Mexico

Deyang Nyandak
Cambridge Health Alliance

GENERAL SURGERY

Nelly-Ange Kontchou
Vanderbilt University Medical Center

Gregory Leya
Massachusetts General Hospital

Camille Mathey-Andrews
Massachusetts General Hospital

Jason Mitchell
Massachusetts General Hospital

Jessica Mueller
Massachusetts General Hospital

Kathryn Taylor
Stanford University Programs

INTERNAL MEDICINE

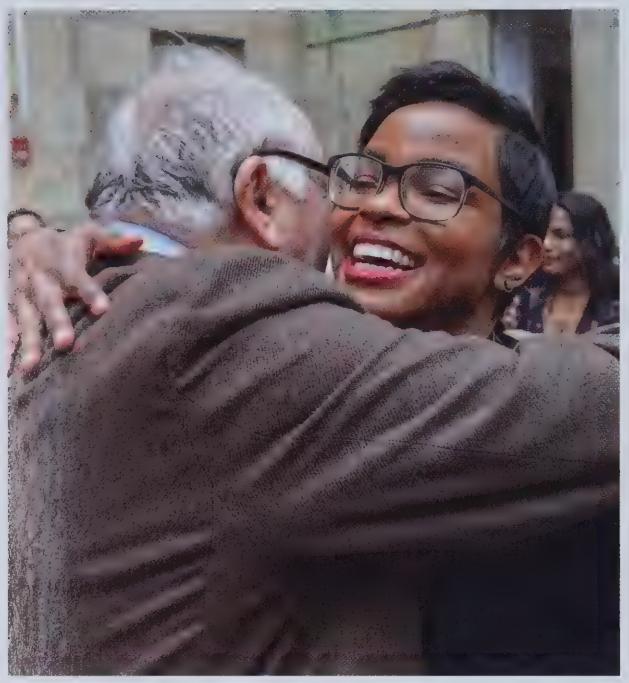
Mohammad Abbasi
Massachusetts General Hospital

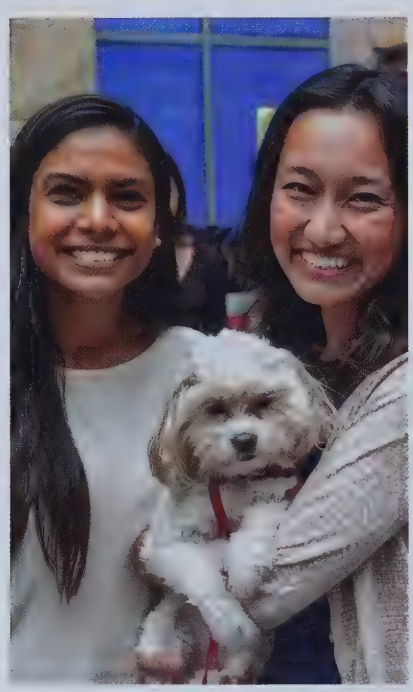
Jordan Anderson
Brigham and Women's Hospital

Aditya Ashok
Johns Hopkins Hospital

Yuyin Chen
New York-Presbyterian Hospital/Weill Cornell Medical Center

Bradley Collins
New York-Presbyterian Hospital/Columbia University Medical Center





Maria Duarte
University of California San Francisco

Wataru Ebina
New York University School of Medicine

Jeremy Feng
Massachusetts General Hospital

Enrico Ferro
Brigham and Women's Hospital

Benjamin Freedman
Beth Israel Deaconess Medical Center

Omar Gutiérrez
Cleveland Clinic

Saurav Haldar
Johns Hopkins Hospital

Ginger Jiang
Beth Israel Deaconess Medical Center

Charlotte Lee
Massachusetts General Hospital

Sean Legler
University of Minnesota Medical School

Brian Li
Beth Israel Deaconess Medical Center

Jesús Luévano
Massachusetts General Hospital

Tracy Makuvire
Brigham and Women's Hospital

Xiaoli Mi
New York-Presbyterian Hospital/Weill Cornell Medical Center

Ramya Mosarla
Massachusetts General Hospital

Anirudh Nandan
University of California San Francisco

Kelsey Natsuhara
University of California San Francisco

Raymond Parrish
Massachusetts General Hospital

Achyut Patil
Stanford University Programs

Emily Rosen
Stanford University Programs

Abhayjit Singh
University of California San Francisco

Catherine Stoeckle
New York-Presbyterian Hospital/Weill Cornell Medical Center

Fangdi Sun
University of California San Francisco

Rohit Thummalapalli
Johns Hopkins Hospital

David Wang
Brigham and Women's Hospital

Danny Wong
Brigham and Women's Hospital

Amy Yu
Massachusetts General Hospital

Travis Zack
University of California San Francisco

MEDICINE-PRIMARY

John Heintz
Hospital of the University of Pennsylvania

Helen Jack
University of Washington Affiliate Hospital

Alexander Kazberouk
University of California San Francisco

Andrew Kim
University of California San Francisco

Kathleen Miller
Massachusetts General Hospital

Andreas Mitchell
University of California San Francisco

Laura Nicholson
Brigham and Women's Hospital

Dorothy Rimmelin
University of California San Francisco

Thomas Wang
Massachusetts General Hospital

NEUROLOGICAL SURGERY

Jay Kumar
Morsani College of Medicine, University of South Florida

Gabriel Sneh
Yale-New Haven Hospital

NEUROLOGY

Margaret Cochran
Boston Children's Hospital

Rebecca MacRae
Boston Children's Hospital

Joseph Rosenthal
Brigham and Women's Hospital

J. Bradley Segal
Stanford University Programs

Erika Williams
Brigham and Women's Hospital

OB/GYN

Iman Berrahou
University of California San Francisco

Esther Chung
Duke University Medical Center

Olivia Foley
Brigham and Women's Hospital

Gillian Horwitz
New York University School of Medicine

Claire Learmonth
Oregon Health & Science University

Nicola Perlman
Brigham and Women's Hospital

Colleen Sinnott
Brigham and Women's Hospital

Mary Tate
Northwestern McGaw

Emily Unger
University of Washington Affiliate Hospital

Liwen Xu
UCLA Medical Center

OPHTHALMOLOGY

Carolina Chiou
Massachusetts Eye and Ear

Liane Dallalzadeh
University of California San Diego

Benyam Kinde
University of California San Francisco

Connie Sears
Stanford University Programs

Zujaja Tauqeer
Scheie Eye Institute/ University of Pennsylvania

ORAL AND MAXILLOFACIAL SURGERY

Austin Be
Massachusetts General Hospital

Sarav Patel
Massachusetts General Hospital

ORTHOPEDIC SURGERY

Jennifer Bido
Hospital for Special Surgery

Eric Davis
University of North Carolina Hospitals

Leah Demetri
University of California San Francisco

Yuri Pompeu
Hospital for Special Surgery

Prashant Rajan
Cleveland Clinic

Akash Shah
UCLA Medical Center

John Wickman
Duke University Medical Center

Mark Wu
Duke University Medical Center

PATHOLOGY

Matthew Canver
New York-Presbyterian Hospital/Weill Cornell Medical Center

Wilfredo Garcia Beltrán
Massachusetts General Hospital

Alireza Samiei
UCLA Medical Center

PEDIATRICS

Nora Abo-Sido
Massachusetts General Hospital

Elorm Avakame
Children's Hospital Medical Center

Alexis Ball
University of Colorado School of Medicine

Melanie Baskind
University of California San Francisco

Anne Berens
University of California San Francisco

Walter Chen
Boston Children's Hospital

Alissa D'Gama
Boston Children's Hospital

Frank Gonzalez
Boston Children's Hospital

Julie Gonzalez
Johns Hopkins Hospital

Ioannis Kalogirou Valtis
Brigham and Women's Hospital

Ye jin Kang
University of Texas Southwestern Medical School

Naveed Rabbani
University of Washington Affiliate Hospital

Victoria Robson
Boston Children's Hospital

Jessica Ruiz
Boston Children's Hospital

Kristan Scott
Boston Children's Hospital

Yongtian Tan
University of California San Francisco

PHYSICAL MEDICINE AND REHABILITATION

Cristina Shea
Spaulding Rehabilitation Hospital

PLASTIC SURGERY

David Chi
Barnes-Jewish Hospital

Anne Huang
University of Chicago Medical Center

Ethan MacKenzie
University of Wisconsin Hospital and Clinics

Marvee Turk
University of Southern California

PSYCHIATRY

Ryan Dosumu-Johnson
New York-Presbyterian Hospital/ Columbia University Medical Center

Michal McDowell
Massachusetts General Hospital

Alexander Moscicki
Massachusetts General Hospital

William Smith
University of California San Francisco

Ivana Viani
Brigham and Women's Hospital

Belinda Wang
University of California San Francisco

Shuyu Wang
University of California San Francisco

RADIATION ONCOLOGY

Eric Bent
Massachusetts General Hospital

Kevin Diao
University of Texas MD Anderson Cancer Center

Leith Hathout
San Diego Medical Center

Harper Hubbeling
Memorial Sloan Kettering

Kevin Liu
Massachusetts General Hospital

Michael Milligan
Massachusetts General Hospital

Anthony Nguyen
Cedars-Sinai Medical Center

Ryan Park
Massachusetts General Hospital

Emily Schapira
Memorial Sloan Kettering

Diana Shi
Massachusetts General Hospital

Horatio Thomas
University of California San Francisco

David Yang
Massachusetts General Hospital

RADIOLOGY

Hena Ahmed
Hospital of the University of Pennsylvania

Emmanuel Carrodeguas
University of California San Francisco

Imarhia Enogieru
Duke University Medical Center

Perry Hampilos
Massachusetts General Hospital

Meng Hao
Hospital of the University of Pennsylvania

Masis Isikbay
University of California San Francisco

Joshua Ladner
Madigan Army Medical Center

Mihan Lee
New York-Presbyterian Hospital/Weill Cornell Medical Center

Derek Peters
Duke University Medical Center

Anji Tang
Brigham and Women's Hospital

Debra Whorms
Hospital of the University of Pennsylvania

UROLOGY

Eileen Brandes
Dartmouth-Hitchcock Medical Center

Graham Lieberman
Massachusetts General Hospital

VASCULAR SURGERY

Elise DeRoo
University of Wisconsin Hospital and Clinics

Chloé Powell
University of Michigan Hospital

OTHER

Michael Coulter
Postdoctoral Fellow
University of California San Francisco
Center for Integrative Neuroscience

Gabriel Friedman
Neurological Surgery
Massachusetts General Hospital

Madelyn Ho
Dancer
Paul Taylor Dance Company

Xinli Hu
Human Genetics
Pfizer Inc.

Kristin Knouse
Fellow
Whitehead Institute

Peter Renehan
Healthcare M&A Associate
Lazard Frères & Co.

Robert Smalley
Diagnostic Residency
Naval Medical Center Portsmouth

Institutions listed represent categorical residency matches and their locations. Locations of preliminary or transitional programs are not included.

PRESIDENT'S REPORT

A Council Year Ends—and **Begins**

THIS SPRING, A RECORD NUMBER OF ALUMNI AND GUESTS returned for Reunion and Alumni Day. Highlights included the scientific symposium; the 25th reunion symposium, which focused on finding joy in the profession; a reception for students and alumni underrepresented in medicine; student-led campus tours; a recent-graduates party; and a family picnic by the Charles River. The weather was perfect, showcasing the flowering trees and plants on campus and throughout Boston.

It was great to see many of you at the Harvard Medical Alumni Association's annual business meeting, where I shared updates on the Alumni Council's work this year. I also was pleased to announce the Council's newly elected members, Joanna "Mimi" Choi, MD '09, from Los Angeles (second pentad); Allison McDonough, MD '97, from Newton, Massachusetts (fifth pentad); Ted Kohler, MD '76, from Mercer Island, Washington (ninth pentad); and Alfred Sommer, MD '67, from Baltimore (councilor at large).

On May 23, at our third and final meeting of the academic year, members of the Council accomplished several critical goals and heard updates on key HMS initiatives, including:

- agreeing, unanimously, to adjust class-year affiliations to align alumni with classmates they entered HMS with, rather than the class they graduated with
- finalizing a survey to be sent to all alumni to evaluate and identify ways to improve medical education at HMS, a project launched in anticipation of the upcoming visit from the Liaison Committee on Medical Education (LCME). Please look for this very brief survey this summer. A high rate of participation is important, and there is an opportunity to add suggestions and comments to guide the School's future.
- hearing from Dean George Daley, MD '91, and Chief Financial Officer Michael White on the financial status of HMS and plans underway to address the deficit
- enjoying selected performances from FABRIC, the first-year students' show. FABRIC was started by students 18 years ago as part of Revisit Week. It celebrates the diversity, passions, and talents of our amazing medical students.

Please remember that your HMS alumni benefits include access to Countway Library online holdings, use of a University-wide alumni directory, periodic discounts on CME courses, and global education opportunities through the External Education program. To get involved in reunion planning or to learn more about your alumni benefits, contact the Office of Alumni Affairs and Development at hmsalum@hms.harvard.edu.

Elizabeth (Lisa) Petri Henske, MD '85, is an HMS professor of medicine at Brigham and Women's Hospital, director of the Center for LAM Research and Clinical Care at Brigham and Women's, director of the Brigham Research Institute, associate member of the Broad Institute of MIT and Harvard, and a medical oncologist at the Lank Center for Genitourinary Oncology at Dana-Farber Cancer Institute.

Alumni Announcements

Preferred class years

A number of alumni who spent more than four years at HMS have been asking Alumni Affairs to affiliate them with their first-year classmates. As a result, the Alumni Council recently voted to adjust the preferred class years of all current and future alumni to be four years after their start date, regardless of their actual graduation year. Alumni affected by this change were notified by email and by a postcard mailed this summer.

Volunteer to advise a student

Alumni are invited to sign up to advise students on their careers. Volunteers can meet with students in person or communicate by email or phone to help provide guidance on topics ranging from specialties to residencies, as well as help with mock internship interviews. Interested alumni should contact Dea Angiolillo, MD '79, at **dea_angiolillo@hms.harvard.edu**.

Electronic journal access

Alumni have online access to thousands of peer-reviewed journals and more than 2,000 seminars. Visit **alumni.hms.harvard.edu/online-journals** to access the available collections.

Alumni reception in Austin

If you live in the Austin area or are planning to attend the Association of American Medical Colleges (AAMC) annual conference there, don't miss the HMS alumni reception on Saturday, November 3, from 6:30-7:45 p.m., at the JW Marriott Austin. For more information or to RSVP, call 617-384-8522 or email **hmsalum@hms.harvard.edu**.

Reunion: Save the date

Alumni from HMS classes ending in 4 and 9 and their guests are invited to rediscover campus and rekindle friendships during the Reunion 2019 festivities, June 6-8, 2019. Visit **alumni.hms.harvard.edu/reunion** for the latest details. Reunion Report submissions will open in late September.

RANDY GLASS

HARVARD MEDICAL SCHOOL

"My gift reassures me that I have some part in the future and excellence of Harvard Medical School."

— Martin Mihm Jr., MD
Director, Mihm Cutaneous Pathology Consultative Service
Director, Melanoma Program, Department of Dermatology
Brigham and Women's Hospital

A LASTING LEGACY

Martin Mihm has been a member of the Harvard Medical community since the 1960s when he was a dermatology resident at Massachusetts General Hospital. In addition to significant donations, he has included HMS in his estate plans to leave his mark on the institution that has been such an important part of his life.

JOIN HIM IN LEAVING A LEGACY AT HMS.

BEQUESTS | CHARITABLE TRUSTS | GIFT ANNUITIES | REAL ESTATE | RETIREMENT PLAN ASSETS

A GIFT TO HMS THROUGH YOUR WILL OR TRUST IS ONE OF THE SIMPLEST WAYS TO LEAVE A LEGACY.

Learn more at
hms.harvard.edu/bequests

Or contact a member of our Gift Planning team in confidence:
1-800-922-1782

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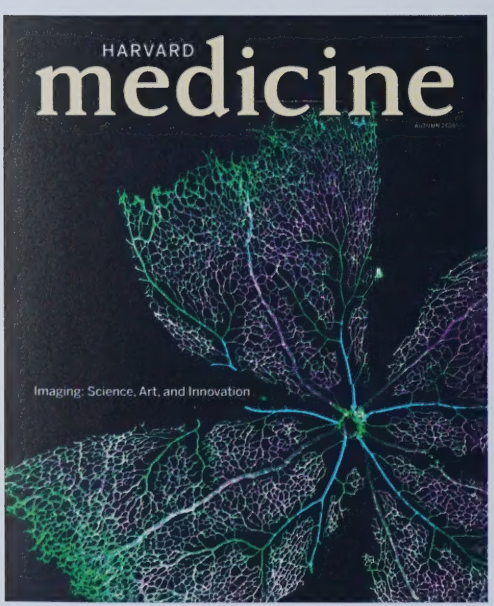
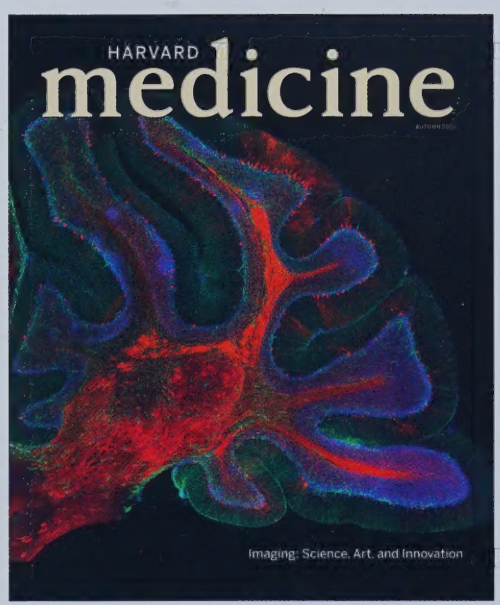
The Colors of Autumn

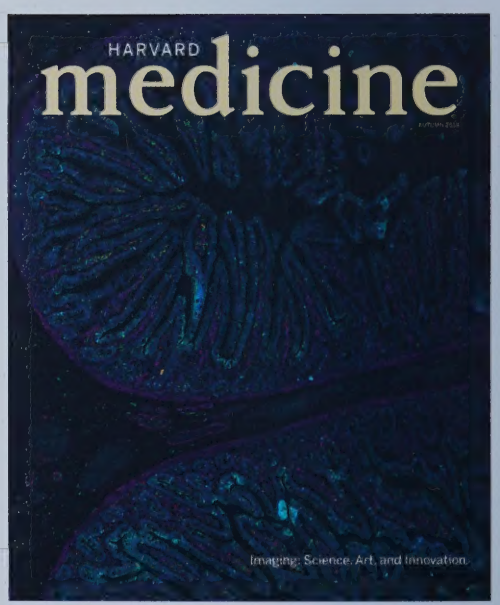
In the spring of this year, faculty, trainees, and students in HMS research labs were invited to submit images showing the beauty of the worlds they study. The winning entries grace the three different covers of this issue of *Harvard Medicine* magazine.



The blood-retinal barrier in a mouse
Photo by: Brian Chow, graduate student
Principal investigator: Chenghua Gu, professor of neurobiology



The cerebellum of the brain
Photo by: David Brann, graduate student
Principal investigator: Sandeep Datta, associate professor of neurobiology



The human small intestine
Photo by: Zoltan Maliga, senior research scientist
Principal investigator: Peter Sorger, Otto Krayer Professor of Systems Pharmacology